Decision Memo for Continuous Positive Airway Pressure (CPAP) Therapy for Obstructive Sleep Apnea (OSA) (CAG-00093R2)

Decision Summary

We received a request to reconsider the 2005 National Coverage Determination (NCD) for CPAP Therapy for OSA (CAG-00093R) to allow coverage of CPAP based upon a diagnosis of OSA by home sleep testing (HST). After considering public comments and additional information, we are making the following changes to the NCD for CPAP. The revised indications and limitations NCD are noted in Appendix B.

1.

Coverage of CPAP is initially limited to a 12 week period for beneficiaries diagnosed with OSA as subsequently described. CPAP is subsequently covered for those beneficiaries diagnosed with OSA whose OSA improved as a result of CPAP during this 12 week period.

We remind the reader that Durable Medical Equipment, Prosthetics, Orthotics, and Supplies (DMEPOS) suppliers are required to provide beneficiaries with necessary information and instructions on how to use Medicare-covered items safely and effectively. 42 CFR 424.57(c)(12). Failure to meet this standard may result in revocation of the DMEPOS supplier's billing privileges. 42 CFR 424.57(d).

2.

CPAP for adults is covered when diagnosed using a clinical evaluation and a positive:

a. polysomnography (PSG) performed in a sleep laboratory; or
b. unattended home sleep monitoring device of Type II; or
c. unattended home sleep monitoring device of Type III; or
d. unattended home sleep monitoring device of Type IV, measuring at least three channels

We remind the reader that, in general, pursuant to 42 CFR 410.32(a) diagnostic tests that are not ordered by the beneficiary's treating physician are not considered reasonable and necessary. Pursuant to 42 CFR 410.32(b) diagnostic tests payable under the physician fee schedule that are furnished without the required level of supervision by a physician are not reasonable and necessary.

3. A positive test for OSA is established if either of the following criterion using the Apnea-Hypopnea Index (AHI) or Respiratory Disturbance Index (RDI) are met:

- AHI or RDI greater than or equal to 15 events per hour, or
- AHI or RDI greater than or equal to 5 and less than or equal to 14 events per hour with documented symptoms of excessive daytime sleepiness, impaired cognition, mood disorders or insomnia, or documented hypertension, ischemic heart disease, or history of stroke.

The AHI is equal to the average number of episodes of apnea and hypopnea per hour. The RDI is equal to the average number of respiratory disturbances per hour.

4. If the AHI or RDI is calculated based on less than two hours of continuous recorded sleep, the total number of recorded events to calculate the AHI or RDI during sleep testing is at least the number of events that would have been required in a two hour period.

5. We are deleting the distinct requirements that an individual have moderate to severe OSA and that surgery is a likely alternative.

6. CPAP based on clinical diagnosis alone or using a diagnostic procedure other than PSG or Type II, Type III, or a Type IV HST measuring at least three channels is covered only when provided in the context of a clinical study when that study meets the following standards:

   A clinical study seeking Medicare payment for CPAP provided to the beneficiary pursuant to Coverage with Evidence Development (CED) must address one or more of the following questions:

   a. In Medicare aged subjects with clinically identified risk factors for OSA, how does the diagnostic accuracy of a clinical trial of CPAP compare with PSG and Type II, III & IV HST in identifying subjects with OSA who will respond to CPAP?
   b. In Medicare aged subjects with clinically identified risk factors for OSA who have not undergone confirmatory testing with PSG or Type II, III & IV HST, does CPAP cause clinically meaningful harm?

      The study must meet the following additional standards:

c. The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.
d. The research study is well-supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
e. The research study does not unjustifiably duplicate existing studies.
f. The research study design is appropriate to answer the research question being asked in the study.
g. The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
h. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it also must be in compliance with 21 CFR Parts 50 and 56.
i. All aspects of the research study are conducted according to the appropriate standards of scientific integrity.
j. The research study has a written protocol that clearly addresses, or incorporates by reference, the Medicare standards.
k. The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life-threatening as defined in 21 CFR § 312.81(a) and the patient has no other viable treatment options.
l. The clinical research study is registered on the ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.
m. The research study protocol specifies the method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. However, a full report of the outcomes must be made public no later than three (3) years after the end of data collection.
n. The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria affect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.

o. The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Social Security Act (the Act), the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that the Centers for Medicare and Medicaid Services (CMS) determines meet the above-listed standards and address the above-listed research questions

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Decision Memo

TO: Administrative File: CAG #00093R2 Continuous Positive Airway Pressure (CPAP) Therapy for Obstructive Sleep Apnea (OSA)

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SUBJECT: Coverage Decision Memorandum for Continuous Positive Airway Pressure (CPAP) Therapy for Obstructive Sleep Apnea (OSA) (CAG-00093R2)

DATE: March 13, 2008

I. Decision

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II. Background

We use the abbreviation PSG to refer to attended polysomnography or an attended polysomnogram depending on the context of the sentence, unless we specifically describe an unattended use. We use the abbreviation HST to refer to unattended multichannel home sleep testing or multichannel home sleep monitoring.

OSA, sometimes referred to as Obstructive Sleep Apnea Hypopnea Syndrome-OSAHS, is associated with significant morbidity and mortality. It is a commonly underdiagnosed condition that occurs in 4% of men and 2% of women (Young et al. 1993). The prevalence increases with age (up to 10% in persons 65 and older), as well as with increased weight. Complications associated with OSA include excessive daytime sleepiness, concentration difficulty, coronary artery disease, and stroke (Kokturk et al. 2005). It is estimated that 10% of patients with congestive heart failure (CHF) have OSA, which is independently associated with systemic arterial hypertension (Caples et al. 2005). Untreated OSA is associated with a ten-fold increased risk of motor vehicle accidents (Teran-Santos et al. 1999). The most common clinical presentation of patients with OSA is obesity accompanied by excessive daytime drowsiness (20% of adults with Body Mass Index (BMI) > 30 have OSA), although other clinical findings associated with OSA include nocturnal choking or gasping, witnessed apneas during sleep, large neck circumference and daytime fatigue.

Of the three different forms of sleep apnea (obstructive, central, or mixed), OSA is the most common. Patients suffering with sleep apnea may literally stop breathing (apnea) or have decreased breathing (hypopnea), repeatedly during sleep. The apnea episodes often last for a minute or longer, and can occur hundreds of times during a single night's sleep. During the obstructive apnea episodes, either complete or partial obstruction of the airway occurs. The anatomic site of obstruction is thought to be the soft palate, extending to the base of the tongue. When patients with OSA fall asleep, muscles of this region relax to the point of permitting airway collapse and obstruction. When the airway closes, breathing stops and the sleeper awakens to open the airway. Arousals from sleep usually last only a few seconds, but these brief arousals disrupt continuous sleep and prevent persons from reaching deep stages of sleep (e.g., rapid eye movement sleep-REM), which is necessary in order for the body to rest and replenish strength. The patient repeats this cycle throughout the sleep period.

Diagnosis

OSA has been often defined by an AHI of $\geq$ 5 events per hour during sleep (when using this less restrictive definition, the prevalence may be as high as 25% of the population) or by a higher threshold e.g. AHI of $\geq$ 15 events per hour (the prevalence is as reported above). Medicare has covered CPAP for the treatment of OSA if the beneficiary has an AHI greater than or equal to 5 events and less than or equal to 14 events per hour with a co-morbidity related to OSA, or an AHI $\geq$ 15 events per hour without a co-morbidity related to OSA. The key diagnostic finding in OSA is episodes of airflow cessation or reduction at the nose and mouth despite evidence of continuing respiratory effort.

Other common clinical findings used by physicians in the diagnosis of OSA include oxygen desaturation, abnormal oxygen desaturation index, and RDI which represents the total number of apneas and hypopneas in the total sleep period divided by the total number of hours in the sleep period. There is no universally accepted definition of either oxygen desaturation or abnormal oxygen desaturation index in sleep-disordered breathing. Other measures such as arterial pulsatile volume changes, measurement of airflow, measurement of breathing patterns, Multiple Sleep Latency Testing (MSLT) and Maintenance of Wakefulness Testing, computerized electroencephalogram (EEG) analysis, autonomic arousal detection, and body movement analysis are some of the measures currently being employed by physicians for diagnosis of OSA.

Diagnostic tests for OSA have historically been classified into four types. The most comprehensive is designated Type I: attended, or in-facility PSG, which is considered the reference standard for diagnosing OSA. Three categories of portable monitors (used both in attended and unattended settings) have been developed for the diagnosis of OSA. Type II monitors have a minimum of 7 channels (e.g., EEG, EOG, EMG, ECG-heart rate, airflow, respiratory effort, oxygen saturation-this type of device monitors sleep staging, so calculation of AHI can be calculated). Type III monitors have a minimum of 4 monitored channels including ventilation or airflow (at least two channels of respiratory movement or respiratory movement and airflow), heart rate or ECG, and oxygen saturation. Type IV devices do not meet the requirements of other types, and many measure only one or two parameters (e.g., oxygen saturation or airflow) but some Type IV devices measure three or more parameters. There are other technologies that do not readily fall into the classification above.

Overnight PSG is the conventional diagnostic test for OSA. The American Thoracic Society (ATS 1994) and the American Academy of Sleep Medicine (AASM 1997) recommend supervised PSG in the sleep laboratory over 2 nights for the diagnosis of OSA and the initiation of CPAP.

According to Harrison's Principles of Internal Medicine (2005):

…the definitive investigation for suspected OSA is polysomnography (PSG), a detailed overnight sleep study that includes recording of (1) electrographic variables (electroencephalogram, electrooculogram, and submental electromyogram) that permits the identification of sleep and its various phases, (2) ventilatory variables that permit the identification of apneas and their classification as central or obstructive, (3) arterial O2 saturation by ear or finger oximetry, and (4) heart rate."

Young et al. (1999) note limited capacity to provide PSG testing to all persons with symptoms of OSA due to the high prevalence of OSA. Some studies have noted false-negative rates of 14 to 25% (Le Bon et al. 2000; Littner 2000). And as noted by Klingshott et al. (2000) associates, the measures derived from PSG (e.g., AHI) correlate poorly with major consequences of OSA such as sleepiness and cognitive impairment. Loube et al. (1999) and others have also noted that these measures do not reliably predict the response to the standard therapy for OSA, nasal CPAP.

PSG alternatives have been sought. Predictive algorithms (predictive formulae) to determine optimal CPAP (Flemons et al. 1994; Maislin et al. 1995; Rowley et al. 2000), screening oximetry (Whitlaw et al. 2005; Chiner et al. 1999), attended/unattended home diagnostic apnea monitoring devices (Sériés et al 1993; Golpe et al. 2002; Whitelaw et al. 2005), and questionnaires (e.g., Epworth Sleepiness Scale; Sleep Apnea Clinical Scores) have been developed to help make a sensitive and specific diagnosis of OSA. Other strategies that have been suggested to reduce the delay, inconvenience and expense associated with sleep studies include split night studies (Yamashiro et al. 1995), partner titration, and home stepwise titration. These items have been proposed as a diagnostic aid for patients with a high suspicion of OSA (Ballester et al. 2000; Ficker et al. 2001; Ross et al. 1998; Verse Pirsig et al. 2000).

As noted in Harrison's Principles of Internal Medicine:

Because PSG is a time-consuming and expensive test, there is considerable interest in the role of a screening test and of unattended home sleep-monitoring for the investigation of OSA,…in patients with a high probability of OSA (based on history of habitual snoring, nocturnal choking or gasping, witnessed apnea during and daytime sleepiness), overnight recordings of arterial O_2 arterial saturation by oximetry can be used to confirm the diagnosis and obviate the need for full PSG by demonstrating recurrent episode of desaturation (at least 10 to 15 events per hour).

Treatment of OSA

A number of treatment approaches have been recommended for patients with OSA, depending on severity of the disorder (e.g., the degree of clinical symptoms), as well as the objective level of nocturnal respiratory and sleep disturbance (e.g., daytime sleepiness or number of obstructive events per hour of sleep). For patients with severe OSA, nasal CPAP is the treatment of choice. Its regular use improves excessive sleepiness, cognitive performance, and quality of life (Jenkinson et al. 1999; Montserrat et al. 2001). In patients with severe OSA who can not tolerate nasal CPAP, surgical procedures (e.g., uvulopalatopharygnoplasty-UPPP, maxillofacial surgery) may be indicated. In patients with mild to moderate OSA, nasal CPAP may be indicated, though conservative measures such as weight reduction, avoidance of alcohol, avoidance of sleeping in a recumbent position, or intra-oral appliances may be better tolerated.

CPAP treatment uses air pressure to maintain airway patency. There are several types of CPAP devices used in the treatment of OSA. These include: (1) conventional CPAP devices which provide a constant, steady air pressure all night; (2) bi-level positive airway pressure devices, which, instead of providing a constant pressure throughout the night, sense inspiration and expiration and vary the level of pressure accordingly; and (3) responsive ("smart") airway pressure devices that incorporate flow and pressure sensors and automatic regulation systems to continuously adjust mask pressure to the actual needs of the patient.

Conventionally, technicians titrate CPAP pressures via a therapeutic mask pressure (i.e. the minimum pressure that eliminates abnormal breathing) as determined by manual titration over the course of a night in a sleep laboratory. But the long-held belief that fixed-pressure CPAP therapy is the standard is being challenged. The pressure required to maintain upper airway patency in patients with OSA varies throughout the night depending on body position (Jokic, Klimaszewski et al. 1999), sleep state and other factors. Also, CPAP requirements may change over time due to changes in upper airway properties as well as variation in body weight.

Alternatively, automatic computer-controlled CPAP titration (auto CPAP) can be performed over one or several nights, attended or unattended (a technician can be present or absent), in a sleep laboratory or a home setting. Auto CPAP devices can be used either for titration only, in order to choose a single therapeutic pressure that will be used on a long-term basis or permanently for adjusting to the patient's changing needs. The use of auto-titrating CPAP based on algorithms has also been evaluated in the treatment of OSA (Berry et al. 2002; Stammnitz et al. 2004). Auto CPAP devices adjust pressure by feed-back control according to patterns of pressure, flow or other signals recorded during treatment. Information obtained on pressure readings during an unattended auto CPAP titration may determine therapeutic pressure for subsequent fixed pressure CPAP. A number of studies have been done which have shown that the use of autotitration CPAP machines, as opposed to fixed-flow CPAP machines, are effective in determining therapeutic CPAP, and as a method of treatment (Berry et al. 2002; Stammnitz et al. 2004; Massie et al. 2003).

III. History of Medicare Coverage

In 1986, the CMS (then known as the Health Care Financing Administration) asked the Office of Health Technology Assessment (OHTA) to conduct an assessment of the safety, clinical effectiveness and use of CPAP. OHTA reported that "the consensus of clinical opinion from the available information appears to be that CPAP can in the majority of cases prevent OSA and provide substantial clinical improvement with minimal associated morbidity." They went on further to recommend that "the use of CPAP be covered under Medicare when used in adult patients with moderate and severe OSA who have failed to obtain relief from other non-invasive therapies and for whom surgery would be the only other therapeutic alternative." The diagnosis of OSA required at least 30 episodes of apnea, each lasting a minimum of 10 seconds, during 6-7 hours of sleep. These specifications were based predominately on expert opinions at the time.

Based on the OHTA technology assessment (TA), Medicare issued an NCD (see NCD Manual 240.4) which covered CPAP for adult patients with moderate or severe OSA for whom surgery is a likely alternative (effective date January 12, 1987) and adopted OHTA's recommendations on the diagnosis of OSA. Unattended HST has been reviewed by CMS since 1989. In 1995, the agency’s reviewing body for the development of NCDs concluded that the safety and effectiveness of home studies used to diagnosis sleep disorders were unproven and thus should not be covered by the Medicare program. The advisory committee recommended that this issue be reconsidered for national policy following the completion of a large study of sleep disorders by the National Institutes of Health. This study was to include an evaluation of in-home testing. The study was expected to be completed within two to three years. Therefore, the coverage of unattended HST was left to carrier discretion.

In 2001, the national coverage policy on CPAP was expanded to include Medicare beneficiaries with an AHI of $\geq$ 15, or an AHI $\geq$ 5 and $\leq$ 14 with documented symptoms of excessive daytime sleepiness, impaired cognition, mood disorders or insomnia, or documented hypertension, ischemic heart disease or history of stroke. However, the policy specified that only PSG done in a facility-based sleep study laboratory could be used to identify patients with OSA.

In 2005, CMS determined that the evidence was not adequate to conclude that the use of unattended portable multi-channel sleep testing with a minimum of 7 monitored channels including EEG, EOG, EMG, ECG or heart rate, airflow, respiratory effort, and oxygen saturation (Type II devices based on the 1994 ASDA classification) was reasonable and necessary in the diagnosis of OSA and these tests remain noncovered for the diagnosis of OSA.

Current Request

CMS reviewed its NCD regarding the diagnosis of patients with OSA requiring CPAP therapy. (NCD 240.4).

CMS received a complete formal written request from the American Academy of Otolaryngology-Head and Neck Surgery to modify this decision to include the use of portable multi-channel HST devices as an alternative to facility-based PSG in the evaluation of OSA.

In addition, CMS received an incomplete request from a Medicare beneficiary, numerous informal requests from stakeholders, and interest from Medicare contractors concerning the criteria for determining the AHI. The current NCD at section 240.4 states in part "…The AHI is equal to the average number of episodes of apnea and hypopnea per hour and must be based on a minimum of 2 hours of sleep recorded by polysomnography using actual recorded hours of sleep (i.e. the AHI may not be extrapolated or projected)." It has been suggested by some that this requirement be changed to "the AHI is equal to the average number of episodes of apnea and hypopnea per hour and must be based on a minimum of 2 hours of sleep or less, if the actual number of AHI episodes recorded is 30 or more in less than 2 hours, recorded by polysomnography using actual recorded hours of sleep" (i.e., the AHI may not be extrapolated or projected).

We are also aware of recently published research suggesting a benefit for the use of CPAP without prior sleep testing in selected populations (trial of CPAP).

The scope of this reconsideration includes all aspects of this prior NCD.

Benefit Category

Medicare is a defined benefit program. All services furnished under the Medicare program must be medically reasonable and necessary, and appropriate for diagnosis and/ or treatment of an illness or injury. Furthermore, physicians and nonphysician practitioners must be authorized by the State in which the services are furnished to render the services. An item or service must fall within a benefit category as a prerequisite to Medicare coverage: § 1812 (Scope of Part A); § 1832 (Scope of Part B); § 1861(s) (Definition of Medical and Other Health Services).

A CPAP device falls within the DME benefit category found at section 1861(s)(6) of the Act. Regulations found at 42 CFR 414.202 describe DME as equipment furnished by a supplier or a home health agency that: (1) can withstand repeated use; (2) is primarily and customarily used to serve a medical purpose; (3) generally is not useful to an individual in the absence of a illness or injury; (4) is appropriate for use in the home.

CMS considers diagnostic testing to be the appropriate coverage category for PSG and multichannel HST.

IV. Timeline of Recent Activities

March 14, 2007	CMS posted a tracking sheet on the website and the initial 30 day public comment period began.
May 29, 2007	CMS announced that it would convene the Medicare Evidence Development and Coverage Advisory Committee (MedCAC) to consider this issue on Tuesday, September 12, 2007 from 7:30 a.m. until 4:30 p.m. EST at CMS, 7500 Security Blvd, Baltimore, MD 21244.

June 25, 2007	CMS posted initial comments received
September 12, 2007	CMS held a MedCAC meeting.
December 14, 2007	CMS published a proposed decision and opened a 30 day public comment period.
January 13, 2008	Public comment period ended

V. FDA Status

HST devices and other similar devices, such as multi-channel HST and other related devices have been considered and cleared for marketing by the FDA under a 510(k) process. The 510(k) is a notification of intent to market a specific device. The FDA has determined that certain HST devices are "substantially equivalent to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act." A substantially equivalent determination assumes compliance with the Good Manufacturing Practice requirements, as set forth in the Quality System Regulation (QS) for Medical Devices: General regulation (21 CFR Part 820) and that, through periodic QS inspections, the FDA will verify such assumptions. Failure to comply with the GMP regulation may result in regulatory action. Typically, no clinical data is required as part of the 510 (k) application, but instead the clearance process focuses on technical performance. However, the FDA does request clinical data for snore validation as well as event detection (i.e. clinical validation that the apneas or hypopneas detected are also scored as apneas or hypopneas by a manual scorer). The FDA also compares sensitivity and positive predictive values to a predicate device.

The FDA has cleared numerous types of CPAP devices for use in the home under the 510(k) process. These include but are not limited to many devices that allow a patient to wear a device that collects airflow and other patient measurements into a device that records data, while treating OSA with that device. The patient then takes the device to the physician and the physician downloads information that determines whether the patient has an apnea sleep -related breathing disorder including OSA or needs further sleep studies or assessment.

VI. General Methodological Principles

When making NCDs, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for Medicare beneficiaries. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary under § 1862(a)(1)(A) of the Act.

A detailed account of the methodological principles of study design that are used to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix A. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, and the blinding of readers of the index test, and reference test results.

Public comment sometimes cites the published clinical evidence and gives CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum.

VII. Evidence

A. Introduction

We are providing a summary of the evidence that we considered during our review. CMS held a MedCAC meeting on September 12, 2007 and commissioned external TAs from the AHRQ to review published clinical evidence on the use of devices in the diagnosis of OSA and to do modeling of different scenarios of diagnosis. CMS reviewed information and recommendations provided as a result of the MedCAC meeting, the TAs provided by AHRQ, and conducted its own independent search and review of individual clinical studies addressing this issue. CMS also reviewed other information from professional societies and other groups/organizations, searched evidence based practice guidelines, consensus statements, and position papers.

We sought to determine if new evidence supports conclusions that differ from those in the NCD on this topic that we published in early 2005. For HST we focused on evidence published since the 2004 Medicare Coverage Advisory Committee (MCAC) meeting and the 2005 reconsideration of this NCD. Because we had not previously reviewed the evidence pertinent to clinical diagnosis alone, our review of that literature included evidence predating our 2005 decision.

B. Discussion of evidence reviewed

1. Questions & Outcomes

Question 1: Is the evidence adequate to determine that diagnostic strategies other than facility based PSG accurately identifies patients with OSA who will benefit from CPAP treatment?

Question 2: Is the evidence adequate to determine that the accurate diagnosis of OSA requires at least two hours continuous recorded sleep?

Question 3: Is diagnosis of OSA by clinical criteria alone sufficient for the use of CPAP in the absence of either a positive PSG or a positive unattended multichannel home sleep test?

As diagnostic tests, PSG and HST would not be expected to directly change health outcomes. Rather, a diagnostic test affects health outcomes through changes in disease management brought about by physician actions taken in response to test results. Such actions may include decisions to treat or withhold treatment, to choose one treatment modality over another, or to choose a different dose or duration of the same treatment. To some extent the usefulness of a test result is constrained by the available treatment options. As noted in the Background section, the number of practical treatment options for OSA is limited. Most patients get CPAP; a few get oral appliances or surgery. A patient whose OSA is not readily controlled with CPAP may seek other treatment, continue CPAP with lesser benefit, or discontinue CPAP and not seek further medical treatment. In addressing the questions above, one of the factors we considered is whether there is sufficient evidence that the incremental information derived from PSG or HST leads to improved treatment of OSA by causing physicians to prescribe a different treatment than they would have prescribed without access to the test results.

The choice of specific treatment is influenced by many factors other than its predicted ability to reduce sleep apnea. Some patients may prefer to avoid a surgical intervention. Other patients may have comorbid conditions such as chronic cardiac or respiratory disease that will influence the use or avoidance of certain treatments.

Outcomes of interest for a diagnostic test are not limited to determining its accuracy but also include beneficial or adverse clinical effects, such as changes in management due to test findings or preferably, improved health outcomes for Medicare beneficiaries. Ideally, we would see evidence that the systematic incorporation of PSG or HST results into a treatment algorithm leads treating physicians to prescribe different and better treatment than they would otherwise have prescribed, and that those patients whose treatment is changed by test results remain on the regimen and achieve better long term OSA control documented by repeated assessments over time.

There is no anatomic or physiologic "gold standard" for the diagnosis of OSA, in contrast to conditions such as cancer where a tissue biopsy result is the definitive standard reference. In studies that compare HST to facility-based PSG, the investigators have used the PSG result as the standard reference, i.e. the PSG result is used to define the true disease state for the individual patient. This is less than ideal since the true sensitivity and specificity of PSG in diagnosing OSA is not well documented, and this deficiency poses a practical difficulty in diagnosing OSA. Given the absence of a true "gold standard" reference, the clinical application of terms such as sensitivity and specificity is not straightforward.

Such evidence permits only the comparison of HST to facility-based PSG. It is problematic to make the inferential leap from there to a judgment on the ability of HST or PSG to accurately identify those patients who will, if untreated with CPAP, suffer the morbidity and mortality of OSA. If an individual patient has conflicting results with these two tests, e.g. a negative HST in the face of a positive PSG, there is no available higher reference to determine whether the conflict arises from a false negative HST or a false positive PSG.

2. External TAs

Systematic reviews are based on a comprehensive search of published studies to answer a clearly defined and specific set of clinical questions. A well-defined strategy or protocol (established before the results of the individual studies are known) guides this literature search. Thus, the process of identifying studies for potential inclusion and the sources for finding such articles is explicitly documented at the start of the review. Finally, systematic reviews provide a detailed assessment of the studies included. CMS commissioned two TAs from AHRQ:

- Home diagnosis of OSA-Hypopnea Syndrome, and
- OSA-Hypopnea Syndrome: modeling different diagnostic strategies

We summarize them below. The full reports are available at the following CMS website: http://www.cms.hhs.gov/mcd/viewtechassess.asp?id=204.

Home diagnosis of OSA-Hypopnea Syndrome (OSAHS)

Ninety-three studies were included in a review of the literature. Eligible studies assessed the ability of sleep studies at baseline to predict response to CPAP treatment or CPAP use, the comparison of measurements with portable monitors and facility-based PSG, and the safety of sleep studies.

The TA reported that the reference standard for the diagnosis of OSAHS is facility-based PSG, a comprehensive sleep study that records and evaluates a variety of cardiorespiratory and neurophysiologic signals during sleep time. It quantifies the severity of disturbances with the Apnea-Hypopnea Index (AHI). Higher AHI values imply more severe sleep disturbances. Typically, a value of 15 events/hour of sleep or more is considered to be suggestive of OSAHS. An AHI suggestive of OSAHS is neither sufficient nor necessary for the diagnosis of the condition, as the severity of symptoms has to be accounted for, and other conditions affecting sleep may need to be excluded. Baseline AHI is only modestly associated with response to CPAP or CPAP use among people with high (pre-test) probability for OSAHS. The same is true for other indices obtained from sleep studies such as the mean or minimum O_2 saturation, apnea index, hypopneas index, frequency of arousals and other quantities.

Based on limited data, the authors conclude that type II monitors may identify AHI suggestive of OSAHS with high positive likelihood ratios (> 10) and low negative likelihood ratios (< 0.1) both when the portable monitors were studied in the sleep laboratory and at home. Type III monitors may have the ability to predict AHI suggestive of OSAHS with high positive likelihood ratios and low negative likelihood ratios for various AHI cutoffs in laboratory-based PSG, especially when manual scoring is used. The ability of type III monitors to predict AHI suggestive of OSAHS appears to be better in studies conducted in the specialized sleep unit compared to studies in the home setting. Some studies of type IV monitors also showed high positive likelihood ratios and low negative likelihood ratios, at least for selected sensitivity and specificity pairs from ROC curve analyses. As with type III monitors, the ability of type IV monitors to predict AHI suggestive of OSAHS appears to be better in studies conducted in specialized sleep units. Medicare beneficiaries are older than the studied subjects (the median average age was approximately 50 years in the analyzed studies), and may more often have conditions other than OSAHS that affect sleep (e.g., Periodic Limb Movements in Sleep and Restless Leg Syndrome; cardiac insufficiency). These conditions may be misdiagnosed as OSAHS by sleep monitors that do not record channels necessary for the differential diagnosis from OSAHS. Therefore, some type III and type IV monitors may yield more false positives among Medicare beneficiaries, compared to what was observed in the assessed studies. For studies in the home setting, there are no direct data on whether and to what extent technologist support and patient education affect the comparison of portable monitors with facility-based PSG.

For monitors that may be considered other than Type II, III, or IV the authors found there is insufficient evidence to judge their value in diagnosing OSA. The TA differentiated Type IV monitors with three or more channels from those with one or two channels, finding greater diagnostic ability for the former. We note that the TA reviewed the Watch-PAT100 device as a Type IV device with three or more channels.

OSA-Hypopnea Syndrome: modeling different diagnostic strategies

The TA authors created a model to test the impact of different OSA strategies. When middle-aged people (50 years old) with symptoms and signs suggestive of OSAHS are tested in the home setting, approximately 10 percent of those with OSAHS are expected to remain undiagnosed; approximately 15 percent of those without OSAHS receive false-positive diagnoses. For older adults (70 years old) the expected number of misclassifications is larger, due to the expected increase in false positive diagnoses (30 percent). With the combination strategy that uses home diagnosis and split-night PSG almost 20 percent of middle-aged people with OSAHS received a (false) negative diagnosis, while the proportion of false positive results among 50 year-old people without OSAHS was very low (1 percent). The expected numbers were similar among older adults (70 years old).

Both for middle-aged people and for older adults, the average time spent undiagnosed is practically negligible for the strategies that use home monitoring. In the combination strategy, people with positive diagnosis with the portable monitors receive a final split-night PSG diagnosis within 15 weeks on average.

When diagnosis of OSAHS and treatment initiation are managed outside the sleep laboratories in the home setting, middle-aged people with OSAHS spend on average 10 weeks or 9 percent of the total follow up time in undiagnosed health states. Indicatively, the corresponding mean time delay for middle-aged people is 27 weeks when they are managed with facility-based PSG. This number mainly reflects those with false negative diagnoses, who are never started on CPAP. The same is expected among older adults (70 years old).

With the combination strategy, using home diagnosis and split-night PSG, correctly diagnosed people initiate on CPAP after approximately 15 weeks. However, one fifth of the patients are not diagnosed and, overall, the average time spent while not on CPAP ("high-risk" states) becomes 33 weeks. Similar numbers are expected among older adults who have OSAHS.

3. Internal TAs

Literature Search

CMS performed an extensive literature search utilizing PubMed for randomized controlled trials (RCTs), systematic reviews, and series studies evaluating the use of PSG, HST, CPAP trial, and clinical diagnosis of OSA. The literature search was limited to humans. Though we focused our search on evidence published since the 2004-2005 reconsideration of this NCD we looked at relevant studies before that time frame.
There are currently several proposed mechanisms to diagnosis OSA and determine the need for and benefit of CPAP. These include clinical diagnosis alone, PSG, home testing with various devices and a diagnosis made by using a trial of CPAP. We will address the evidence for each individually.

Clinical Diagnosis

Crocker et al. (1990) studied whether the number of PSGs required for diagnosis of OSA could be reduced in the population. They enrolled 100 consecutive patients (average age 50) screened by family and sleep physicians. The patients were then tested by PSG. A clinical model was created for predicting a diagnosis of OSA as compared to PSG and was applied to the next 114 consecutive patients. The model correctly classified 33 of 36 persons with OSA by correctly predicting an AHI > 15 and it correctly classified 35 of 69 patients by correctly predicting an AHI $\leq$ 15. In the model, BMI, reported apnea, age, and hypertension were statistically significant factors. The model had a sensitivity of 92% for predicting OSA when compared to PSG and a specificity of 51%. The authors concluded that clinical observation might reduce the need for PSG in the diagnosis of OSA by one-third.

Deegan et al. (1996) compared the predictive value of certain clinical features to PSG for a diagnosis of OSA. Two hundred fifty consecutive patients (average age 45) were pre-screened by a physician and had a clinical assessment and administration of a sleep questionnaire, along with PSG. One hundred thirty six (54%) had an AHI $\geq$ 15 (considered positive for a diagnosis of OSA) and 114 (46%) had an AHI < 15 (not considered positive for OSA). Using clinical features and oximetry, 32.4% of patients could be confidently categorized, compared to PSG, as either having a true diagnosis of OSA or not having OSA. Significant factors in the model were BMI, alcohol intake, and age. The authors concluded that clinical observation may reduce the need for PSG in the diagnosis of OSA by approximately one-third.

Haponik et al. (1984) asked whether or not PSG is necessary to assess the presence and severity of sleep-disordered breathing. They enrolled 37 patients (average age 50) with clinically suspected OSA, administered a questionnaire and did PSG testing. Compared to PSG (AHI $\geq$ 15 as cutoff for positive diagnosis of OSA) the clinical testing information had a sensitivity of 64% for a correct diagnosis of OSA and a specificity of 100%. The authors concluded that a single, brief clinical observation alone is an ineffective screening procedure for detecting OSA.

Julià-Serdà et al. (1984) enrolled 225 consecutive referrals to a sleep clinic (average age 45 in the non-OSA group and 52 in the OSA group) with suspected OSA to determine whether or not cephalometry was useful in sparing PSG. All subjects had clinical assessment with an ESS questionnaire, physical exam and history. In addition they also had spirometry, cephalometry, and PSG testing. A statistical model was built to estimate a patient's probability of a correct diagnosis of OSA as compared to PSG (using a cutoff value of AHI $\geq$ 10), based on clinical variables, physical examination, pulse oximetry, cephalometry, and soft palate and uvula measurements. The sensitivity of the model for a correct diagnosis of OSA as compared to PSG was 93% and the specificity was 83%. The authors concluded that cephalometry plus oximetry plus history and physical exam is capable of sparing the need for PSG in diagnosing OSA.

In 99 pre-operative Laparoscopic Adjustable Gastric Banding patients with average age in their four groups ranging from 35 to 44, Dixon et al. (1997) attempted to create a clinical model for predicting a correct diagnosis of OSA as compared to PSG. A thorough sleep history and physical examination were performed, checking for symptoms such as nocturnal choking, waking unrefreshed, morning headaches, excessive daytime sleepiness and poor sleep quality. An ESS was administered and all patients had a PSG test. The PSG was hand scored. For a PSG cutoff of AHI $\geq$ 15, independent predictors for a diagnosis of OSA were observed sleep apnea (the only positive symptom predictor of an AHI $\geq$ 15), male sex, higher BMI, age, fasting insulin and glycosylated hemoglobin A1c. From the model created, a scoring mechanism was established and a score of > 3 had a sensitivity of 89% for a correct diagnosis of OSA as compared to PSG and a specificity of 81% for moderate/severe OSA. The authors concluded that a simple method of predicting OSA in severely obese symptomatic subjects can assist in limiting the use of PSG to those with greater risk

In a rare RCT on the topic of clinical modeling of OSA, Mulgrew et al. (2007) investigated the utility of a diagnostic algorithm in conjunction with ambulatory CPAP titration in initial management of OSA. This open label RCT compared PSG with ambulatory CPAP titration in high-risk patients identified by a diagnostic algorithm in a tertiary referral sleep disorders program. Sixty-eight patients (average age 52 in the PSG group and 55 in the ambulatory group) with a high PSG pretest probability of moderate to severe OSA (AHI $\geq$ 15) were identified by ESS score, Sleep Apnea Clinical Score and oximetry. Patients were randomly assigned to PSG or ambulatory titration using a combination of auto CPAP and overnight oximetry. They were observed for 3 months.

The main outcome measure was AHI on CPAP as compared to before CPAP, with secondary outcome measures being ESS score, quality of life and CPAP adherence. After 3 months, there was no difference in the primary outcome—AHI on CPAP (median, 3.2 vs. 2.5; difference, 0.8/h)—between the PSG and ambulatory CPAP groups. After 3 months, there were no differences between groups in the secondary outcomes of ESS score, Sleep Apnea Quality of Life Index, and CPAP. Of particular note was that adherence to CPAP therapy was better in the ambulatory group than in the PSG group. The authors concluded that PSG confers no advantage over the ambulatory approach in terms of diagnosis and CPAP titration in initial management of patients with a high probability of OSA. The authors also concluded that the ambulatory approach may improve adherence to treatment and that, when access to PSG is inadequate, the ambulatory approach can expedite treatment. The authors noted that their study was confined to a specific population and that more studies were needed to generalize the conclusions to other populations.

Lim et al. (2006) performed a study to determine if a clinical model could be developed to predict OSA diagnosis from clinical diagnosis only. Seventy-one consecutive snorers (average age 44) referred for an evaluation for OSA were enrolled. OSA status was determined by clinical assessment based on symptoms suggestive of OSA as well as an ESS and BMI measurement. A PSG was administered and a clinical assessment model was created and used in identifying the ‘non-apneic snorers’ among patients referred with snoring. The model made use of the ESS score (using a cutoff of $\geq$ 15), the BMI (using a cutoff of $\geq$ 28), and the presence of symptoms such as nocturnal choking, witnessed apnea, daytime hypersomnolence or morning headaches. Compared to PSG using a cutoff of AHI > 10, the model had a sensitivity of 93.4% and a specificity of 60% for correctly diagnosing OSA. The authors concluded that identifying ‘non-apneic snorers’ in whom PSG could be avoided can be correctly accomplished via a clinical assessment if two out of three of the following are absent: 1) ESS score $\geq$ 15; 2) a BMI $\geq$ 28; and 3) the presence of specified symptoms such as nocturnal choking, witnessed apnea, daytime hypersomnolence or morning headaches.

Hoffstein et al. (2006) utilized data from 594 patients with an average age 47 who were referred to sleep clinic for suspicion of sleep apnea and were all seen by the same physician to determine if it was possible to develop a clinical model to predict a correct diagnosis of OSA from a clinical exam. A PSG with a cutoff of AHI > 10 was used for the diagnosis of OSA. The independent predictors of a correct diagnosis of OSA as compared to PSG were age, sex, BMI, partner observation of apnea and pharyngeal exam findings (normal vs abnormal). Compared to PSG, the subjective (clinical) impression alone showed a sensitivity of 63% for a correct diagnosis of OSA and a specificity of 60%. The authors concluded that subjective impression alone is not enough to reliably identify patients with or without a correct diagnosis of OSA as compared to PSG.

Garcia et al. (2003) studied whether or not they could predict a correct diagnosis of OSA with a clinical model. They enrolled 227 consecutive patients (average age 58) measuring clinical signs and symptoms and performing a PSG. They then took the next 102 patients and tested their model for clinical diagnosis of OSA (total 329). They utilized an AHI $\geq$ 30 as a cutoff for a correct diagnosis of OSA. In the model created, they utilized a cut point of 11 for the ESS and of 30 for BMI and included other significant and independent factors of age, sex, BMI, neck circumference history and the referring physician's subjective feeling (dichotomized into 'yes' or 'no') as to each patient's probability of having an AHI $\geq$ 30. Compared to PSG, the model had a sensitivity of 80% for a correct diagnosis of OSA and a specificity of 93%. The authors concluded that prior to diagnostic tests for OSA; clinical data can be useful for identifying patients suspected of having AHI $\geq$ 30.

Kushida et al. (1997) attempted to predict OSA with a morphometric predictor model. Thirty patients (age range 15-75) were used to create the model and the model was then prospectively tested on the first consecutive 300 of a total of 423 patients referred for a diagnosis of OSA. All patients were also tested with PSG using a cutoff of AHI $\geq$ 10. The regression model included oral cavity measurements of the palatal height by two separate calipers measuring the distance between the mesial surfaces of the crowns of the second molars to obtain either the maxillary intermolar distance or the mandibular intermolar distance. BMI and neck circumference measurements were also made. The morphometric model had a sensitivity of 97.6% for a correct diagnosis of OSA as compared to PSG and a specificity of 100%. The authors concluded that the model may be clinically useful as a screening tool for OSA rather than as a replacement for PSG.

To see which snorers referred to a sleep laboratory need PSG for the diagnosis of OSA, Rauscher et al. (1993) enrolled 98 habitual snorers and 89 patients (average age 58 overall) with a positive diagnosis of OSA by PSG. A regression model was created that included weight, height, sex, witnessed episodes of apnea and falling asleep reading. This model was applied to 116 consecutive patients referred for investigation of heavy snoring. All patients with negative oximetry and a probability value < 0.31 for having OSA had an AHI < 10 by PSG. The authors concluded that snorers with negative oximetry classified as not having OSA by this model do not need PSG.

Viner et al. (1994) examined whether or not history and physical examination can predict a correct diagnosis of OSA as compared to PSG. They enrolled 410 patients (average age 50) referred for clinically suspected OSA. They conducted a blinded comparison of history and physical examination versus results of nocturnal PSG utilizing a cutoff point of AHI $\geq$ 10. The regression model created included as significant independent factors age, BMI, sex, witnessed episodes of apnea and falling asleep reading. They noted that for $p < 0.20$ (a predicted probability of less than 20% of having OSA) the clinical model had 94% sensitivity and 28% specificity of correctly predicting a diagnosis of OSA as compared to PSG. Subjective impression alone had a sensitivity of 52% and a specificity of 70% for correctly predicting a diagnosis of OSA as compared to PSG. The authors concluded that in patients with a low predicted probability of having a correct diagnosis of OSA, approximately one-third do not need a PSG for diagnosis.

Tsai et al. (2002) performed a study to create a decision rule for diagnostic testing in OSA. They enrolled 75 patients (average age 47) referred to a sleep clinic for suspicion of sleep apnea. No mention of consecutive selection was made. Each patient had portable RDI testing (using a cutoff of RDI $\geq$ 10) and nocturnal oxygen saturation measurements. During the feasibility phase, patients underwent routine clinical assessment plus the upper airway physical examination protocol (UAPP), performed by two investigators. Unreliable or time consuming measurements were eliminated from the UAPP based on clinical judgments and history of snoring and body position based on the consensus of the two investigators. A decision rule was developed using three predictors: a cricomental space (the perpendicular distance between the midpoint of the cricomental line, a straight line from the chin to the cricothyroid cartilage, and the skin of the neck) of 1.5 cm or less, a pharyngeal grade (I = palatopharyngeal arch intersects at the edge of the tongue; II = palatopharyngeal arch intersects at 25% or more of the tongue diameter; III = palatopharyngeal arch intersects at 50% or more of the tongue diameter; IV = palatopharyngeal arch intersects at 75% or more of the tongue diameter) of more than II and the presence of overbite. For patients with all 3 predictors (17%), the decision rule had a PPV of 95% and an NPV of 49% for a true diagnosis of OSA by PSG. Comparable performance was obtained in a validation sample of 50 patients referred for diagnostic testing. The authors concluded that their decision rule provides a simple, reliable and accurate method of identifying a subset of patients with and, perhaps more importantly, without a true diagnosis of OSA.

To compare clinical assessment with home oximetry in the diagnosis of OSA, Guylay et al. (2006) studied 98 non-consecutive patients referred to a sleep clinic for suspicion of sleep apnea. All patients answered a questionnaire, had a history and physical exam, and had PSG testing using a cutoff value of AHI $\geq$ 15 for diagnosis of OSA. Physicians also independently estimated the likelihood of their patient having a true diagnosis of OSA on PSG testing. Compared to PSG, the independent clinical (physician) assessment had a sensitivity of 79% and a specificity of 50% for correctly diagnosing OSA at the cutoff value of AHI $\geq$ 15. Compared to PSG, oximetry with a desaturation of 2% had a sensitivity of 65% and a specificity of 74% for diagnosing OSA at the cutoff value of AHI $\geq$ 15. For desaturations of 3%, the corresponding sensitivity and specificity were 51% and 90%, respectively. If the percentage of sleep time spent at SaO2 < 90 was $\geq$ 1%, the sensitivity for a true diagnosis of OSA as compared to PSG (AHI $\geq$ 15) was 93% and the specificity was 51%. The authors concluded that being at SaO2 < 90 for < 1% of the time on home oximetry practically excludes OSA.

Pillar et al. (1994) compared a clinical diagnosis of OSA to PSG (cutoff AHI $\geq$ 10). Eighty-six patients (average age 47) referred to a sleep clinic for suspicion of OSA were enrolled. The authors did not mention whether or not the subjects were consecutively enrolled. All patients answered a detailed sleep questionnaire, had a brief physical examination and had PSG testing. Compared to PSG (cutoff AHI $\geq$ 10), a clinical diagnosis of OSA had a sensitivity of 79% and a specificity of 50%. With regards to the model, the independent factors for a true diagnosis of OSA were neck circumference, age, self reporting of apnea and falling asleep unintentionally. Compared to PSG, the sensitivity was 92% and the specificity was only 18%. The authors concluded that clinical evaluation cannot replace PSG.

Laboratory Diagnosis using Polysomnography (Type I)

CMS has previously reviewed the data for diagnosis of OSA using PSG. We are not readdressing that literature in this decision.

Home testing for OSA

Types II, III & IV

CMS reviewed the AHRQ TA assessment above and found no additional evidence on HST for Types II, III & IV devices with the exception of some evidence reviewed below on the Watch-PAT100.

Oximetry
Both PSG and HST have an oximetry component, which monitors oxygen desaturation. A number of authors have claimed that just using the oximetry component alone can help in making a diagnosis of OSA (Nuber et al. 2000; Sériés et al 2005; Sériés et al.1993; Guylay et al. 1993).

As noted above, a number of studies have shown that oximetry measurement helps the diagnostic accuracy of OSA. Sériés et al. (1993) performed one of the earliest studies exploring this relationship. Using 240 consecutive patients with a confirmed (AHI > 10 on PSG) diagnosis of OSA (all were clinically suspected of having OSA because of loud snoring; nocturnal choking and awakenings or apneic events or all three reported by a bedmate; bad sleep quality; and daytime hypersomnolence), they found that oximetry had a 98% sensitivity for diagnosing OSA (AHI > 10), but a specificity of only 48%.

Magalang et al. (2003) explored the relationship between oximetry and OSA. They noted that several quantitative indices derived from overnight pulse oximetry have been used to predict the presence of OSA: (1) number of episodes of oxyhemoglobin desaturations below a threshold-usually a 3% or 4% decline below baseline, (2) the cumulative time spent below an oxyhemoglobin saturation of 90%, and (3) the Δ [delta] index—a measure of the variability of the oxyhemoglobin saturation. The researchers wanted to compare these indices and determine if some combination of these indices predicted an individual's AHI as measured by PSG. Using a derivation group which consisted of 224 consecutive patients, a prediction model was generated based on AHIs from the calculated quantitative indexes. The model was further validated using two groups of consecutive eligible patients (group 1 consisted of 101 patients and group 2 consisted of 191 patients). All patients underwent standard overnight PSG and measurement of arterial oxyhemoglobin (by pulse oximeter).

The major findings of the study revealed that among the different oximetry indices, the Δ index was the best predictor of the presence of OSA, though the number of desaturation events provided similar levels of diagnostic accuracy (sensitivity of a Δ index of > 0.63 in the diagnosis of OSA was 91%, while the specificity was 59%). An aggregation of the model using combinations of all oximetry indices reduced the prediction error ($r^2 = 0.70$, $p < 0.05$) compared to using the Δ index alone ($r^2 = 0.60$), improving the precision of prediction of the AHI. The correlation between the predicted and actual AHI was 0.77 when using the Δ index alone, but improved to 0.83 when using a combination of all three oximetry indices. The authors note that one limitation of the study is that the prediction model was validated using overnight pulse oximetry obtained simultaneously with PSG data in the sleep laboratory. However, one advantage of this approach is it eliminated the potential confounder of night-to-night variability of AHI, as well ensuring that oximetry data were collected in exactly the same environment as the PSG data.

Vazquez et al. (2000) studied the diagnostic performance of an automated digital oximetry analysis based on falls and recovery of oxygen saturation and compared the results to PSG. After excluding subjects not eligible for the study, 241 participants with suspected OSA were enrolled in the study and randomly assigned to either PSG or automated off-line analysis of the digitally recorded oximetry signal. Study outcomes included PSG-derived AHI, and oximeter-derived respiratory disturbance index (RDI). The study revealed that the PSG-derived AHI and the oximetry-derived RDI were strongly correlated (R = 0.97); the mean (± 2SD) of the differences between AHI and RDI was 2.18 (± 12.34)/h. Using a case definition of 15 episodes/hour for both AHI and RDI, the sensitivity and specificity were 98% and 88% respectively. The authors noted that one limitation of the applicability of this study was that the algorithm was evaluated by comparison with simultaneous PSGs. They also commented that a number of studies have shown a difference in RDI between home and hospital settings, despite using the same monitor and controlling for technical difficulty. But the authors were quick to note that by evaluating patients in the sleep laboratory, potential confounders (such as technical difficulties associated with remote monitoring, night-to-night variability, and the effects of the home environment on RDI) are eliminated.

Other

We were asked to perform a separate review of the Watch-PAT100 device, as there has been some uncertainty expressed about how to classify this device in the current Type schema. Watch-PAT100 is a HST device which measures the peripheral arterial tone (PAT) and actigraphy (a measure of movement) which are recorded with an ambulatory wrist-worn device (Watch-PAT100). The PAT signal is a measure of the pulsatile volume changes at the finger tip reflecting sympathetic tone variations. The algorithm was developed using a training set of 30 patients recorded simultaneously with PSG and Watch-PAT100. The Watch-PAT100 indirectly detects apnea/hypopnea events by identifying surges of sympathetic activation associated with the termination of these events. This information is further combined with heart rate and pulse oximetry data that are analyzed by the automatic algorithm of the system. This detects respiratory events and calculates the PAT RDI (PRDI).

We found 19 separate articles, papers, editorials, and fact sheets addressing this technology. Of these, CMS determined that 13 were not relevant due to qualities pertaining to sample size, type of evidence, having not been published in a peer reviewed journal or not relevant to this data needed for this NCD. The remaining 6 are reviewed below.

Pittman et al. (2004) aimed at assessing the accuracy of a wrist-worn device (Watch-PAT 100) to diagnose OSA in the home. Participants were not consecutive patients but were a sample of patients who disclosed on a comprehensive questionnaire between June and December of 2002 that they were interested in being contacted about research studies conducted at the sleep laboratory. All 30 subjects completed 2 overnight diagnostic studies with the test device: 1 night in the laboratory with concurrent polysomnography and 1 night in the home with only the Watch-PAT100. The mean age of these subjects was 43.2 ± 10.8 years and mean body mass index was 33.9 ± 7.1 kg/m2. The mean Epworth Sleepiness Scale score was 9.2 ± 4.7 (range 2-18). The order of the laboratory and home study nights was random. The frequency of respiratory events on the PSG was quantified using indexes based on 2 definitions of hypopnea: the respiratory disturbance index (RDI) using American Academy of Sleep Medicine (AASM) Task Force criteria for clinical research, and the Medicare guidelines. The PRDI and oxygen desaturation index (PAT ODI) were then evaluated against the polysomnography AASM guidelines (RDI.C) and Medicare guidelines (RDI.M), respectively, for both Watch-PAT100 diagnostic nights, yielding in-lab and home comparisons. The setting for the PSGs was a sleep laboratory affiliated with a tertiary-care academic medical center. The PSG and PAT measures were compared using the mean [2 SD] of the differences and the intra-class correlation coefficient (ICC). The receiver-operator characteristic curve was used to assess optimum sensitivity and specificity and calculate likelihood ratios. For the in-lab comparison, there was high concordance between:

RDI.C and PAT RDI: ICC = 0.88, mean difference 2.5 [18.9] events per hour

RDI.M and PAT ODI: ICC = 0.95, mean difference 1.4 [12.9] events per hour
sleep time: ICC = 0.70, mean difference 7.0 [93.1] minutes

For the home-laboratory comparison, there was good concordance between:
RDI.C and PAT RDI: ICC = 0.72, mean difference 1.4 [30.1] events per hour
RDI.M and PAT ODI: ICC = 0.80, mean difference 1.6 [26.4] events per hour

Home studies were performed with no technical failures. The authors concluded in this study of a population of 30 patients suspected of having OSA that the Watch-PAT100 can quantify an ODI that compares very well with Medicare criteria for defining respiratory events and an RDI that compares favorably with AASM criteria for defining respiratory events. They further believe that the device can be used with a low failure rate for single use in the lab and home for self-administered testing.

Zou et al. (2006) aimed at assessing the accuracy of a portable monitoring device based on PAT to diagnose OSA (OSA) and to propose a new standard for limited-channel device validation using synchronized polysomnography (PSG) home recordings in a population-based cohort, i.e. in a population sample not preselected for OSA symptoms. The 98 subjects (55 men; age, 60 ± 7 year; body mass index, 28 ± 4 kg/m^2) from a community of 18,000 in Sweden had single-night, unattended PSG and Watch-PAT100 in the home. They were consecutively recruited from the Swedish Skaraborg Hypertension and Diabetes Project. The accuracy of Watch-PAT100 in RDI, AHI, ODI, and sleep-wake detection was assessed by comparison with data from simultaneous PSG recordings.

The mean PSG-AHI in this population was 25.5 ± 22.9 events per hour. The Watch-PAT100 RDI, AHI, and ODI correlated closely (0.88, 0.90, and 0.92; $p < .0001$, respectively) with the corresponding indexes obtained by PSG. The areas under the curve for the receiver-operator characteristic curves for Watch-PAT100 AHI and RDI were 0.93 and 0.90 for the PSG-AHI and RDI thresholds of 10 and 20 ($p < .0001$) respectively. The agreement of the sleep-wake assessment was 82 ± 7%. The authors concluded that the Watch-PAT100 was reasonably accurate for unattended home diagnosis of OSA in a population sample not preselected for OSA symptoms. The authors propose that simultaneous home PSG recordings in population-based cohorts is a reasonable validation standard for assessment of simplified recording tools for OSA diagnosis.

In Pillar et al. (2002), the authors state that arousals from sleep are associated with increased sympathetic activation and are therefore associated with peripheral vasoconstriction. The authors hypothesized that digital vasoconstrictions as measured by peripheral arterial tonometry (PAT), combined with an increase in pulse rate, will accurately reflect arousals from sleep and can provide an autonomic arousal index (AAI). According to the authors, a previously studied group of 40 sleep apnea patients simultaneously recorded by both PSG and PAT systems generated an automated algorithm using the PAT signal (and pulse rate derived from it) was developed for detection of arousals from sleep. This was further validated in this separate group of 96 subjects which included 85 patients referred with suspected OSA and 11 healthy volunteers. All subjects underwent a whole night PSG with simultaneous PAT recording. The PSG recordings were manually (blindly) analyzed for arousals based on American Academy of Sleep Medicine (AASM) criteria, while PAT was scored automatically. There was a significant correlation between PSG and PAT arousals ($R=0.82$, $p<0.0001$) with good agreement across a wide range of values, and with a ROC curve having an area under the curve (AUC) of 0.88. The authors conclude that automated analysis of the peripheral arterial tonometry signal can detect EEG arousals from sleep in a relatively quick and reproducible fashion.

In Bar et al. (2003), the authors aimed at evaluating the efficacy, reliability, and reproducibility of the Watch-PAT100 device for the diagnosis of OSAS as compared to in-laboratory, standard PSG-based manual scoring. One hundred two subjects (69 patients with OSAS and 33 normal non-consecutively selected volunteers) underwent in-laboratory full PSG simultaneously with Watch-PAT100 recording. Fourteen subjects also underwent two additional unattended home sleep studies with the Watch-PAT100 alone. The PSG recordings were blindly scored for apnea/hypopnea according to the American Academy of Sleep Medicine criteria (1999) and the RDI [PSG-RDI] was calculated. The Watch-PAT100 data were analyzed automatically for the PAT RDI (PRDI) by a proprietary algorithm that was the authors reported was previously developed on an independent group of subjects. Across a wide range of RDI levels, the PRDI was highly correlated with the PSG-RDI ($r = 0.88$, $p < 0.0001$), with an area under the receiver operating characteristic curve of 0.82 and 0.87 for thresholds of 10 events per hour and 20 events per hour, respectively. The PRDI scores were also highly reproducible, showing high correlation between home and in-laboratory sleep studies ($r =0.89$, $p < 0.001$). The authors concluded that the Watch-PAT100 may offer an accurate, robust, and reliable ambulatory method for the detection of OSAS with minimal patient discomfort.

Ayas et al. (2003) aimed at assessing the accuracy of a wrist-worn device (Watch-PAT100) to diagnose OSA (OSA). Thirty adult subjects (mean age was 47.0 ± 14.8 years, mean body mass index 31.0 ± 7.6 kg/m2) were recruited through advertisements and from a patient base of those with suspected OSA to participate in this study. The study included patients suspected of having sleep apnea and subjects without suspected sleep apnea. The subjects had simultaneous in-laboratory PSG and wore the Watch-PAT 100 during a full-night recording. PSG sleep and respiratory events were scored according to standard criteria. The mean PSG AHI was 23 ± 23.9 events per hour and the mean PAT AHI 23 ± 15.9 events per hour. There was a significant correlation between the two (r = 0:87, p <0:001). To assess sensitivity and specificity of Watch-PAT100, receiver operator characteristic curves were constructed using a variety of AHI threshold values (10, 15, 20, and 30 events per hour). Optimal combinations of sensitivity and specificity for the various thresholds were 82.6/71.4, 93.3/73.3, 90.9/84.2, and 83.3/91.7, respectively. The authors concluded that the Watch-PAT100 is a device that can detect OSA with reasonable accuracy and that it may be a useful method to diagnose OSA.

In Pillar et al. (2003), the authors stated that they had recently shown that automated analysis of in-lab recorded peripheral arterial tone (PAT) signal and the pulse rate derived from it can accurately assess arousals from sleep as defined by the American Academy of Sleep Medicine (AASM). In the current study they aimed at extending these findings to the Watch-PAT100. They recruited 68 subjects who underwent a whole night PSG with simultaneous recording of PAT signal by the ambulatory Watch-PAT100 device. The PSG recordings were blindly scored via manual analyzing for arousals based on AASM criteria, while PAT was scored automatically based on the algorithm developed previously. The authors determined that was a significant correlation between AASM arousals derived from the PSG and PAT autonomic arousals derived from the Watch-PAT100 (R=0.87, P<0.001), with consistency across a wide range of values of AHI. The sensitivity and specificity of PAT in detecting patients with at least 20 arousals per hour of sleep were 0.80 and 0.79, respectively, with a receiver operating characteristic curve having an area under the curve of 0.87. They concluded that that automatic analysis of peripheral arterial tonometry signal derived from the ambulatory device Watch-PAT100 can accurately identify arousals from sleep in a simple and time saving fashion

Diagnosis of OSA using CPAP

Senn et al. (2006) were one of a number of groups that studied the feasibility of using CPAP to make a diagnosis of OSA in patients with a high-pretest probability of disease. Specifically, using a study of diagnostic accuracy in a university sleep disorder setting, they wanted to evaluate whether the diagnosis of OSA could be inferred from the response to treatment with CPAP (CPAP trial); i.e. whether a CPAP trial predict an AHI $\geq$ 10 on PSG and how successfully OSA patients were treated over a period of 4 or more months. The accuracy of the CPAP trial would be evaluated by comparing results to those of PSGs performed in all patients (for validation) and by comparison to the clinical outcomes of OSA patients after 4 months of treatment with CPAP following a positive trial result. A trial by CPAP was considered positive if, at the end of the followup period, a patient reported using CPAP for 2 or more hours per night and wanted to continue using CPAP. Baseline ESS studies, quality of life measures (SF-36), a questionnaire (Kump), as well as vigilance measures (OSLER test) (Bennett et al. 1997; Jenkinson et al. 1999) were assessed in 76 sleepy snorers consecutively referred for a clinical diagnosis of OSA. A diagnosis of OSA was defined as a mean AHI > 10.

Of the original 195 consecutive patients referred for possible participation in the study, after excluding patients not meeting criteria, 76 patients (100% of those with AHI > 10 fitting criteria, average age 52) were enrolled in the study. Forty-four of 76 patients (58%) had sleep apnea as confirmed by an AHI > 10/h. The CPAP trial predicted sleep apnea with a sensitivity of 80%, a specificity of 97%, and positive and negative predictive values of 97% and 78%, respectively. In 35 of 76 sleep apnea patients (46%) with positive CPAP trial results, polysomnography could have been avoided. These patients were prescribed long-term CPAP therapy. After 4 months, 33 of 35 patients (94%) still used CPAP and their symptoms remained improved. These patients were identified by the CPAP trial with positive and negative predictive values of 92% and 100%, respectively. The authors concluded that CPAP is a "pragmatic" approach to identify OSA patients with "CPAP-responsive disease" who benefit from long-term CPAP therapy. They further concluded that in a selected population, a trial of CPAP may help to diagnose OSA, identify patients who benefit from CPAP and reduce the need for polysomnography. Furthermore, long-term CPAP therapy can be established without the need for PSG.

Limitations of the study according to the authors included patients designated as being "false positive" and exhibiting a placebo effect from CPAP. Results may not be generalizable to the Medicare population since by figures given in the paper approximately one-sixth of the subjects were 65 years or older.

Some proponents of CPAP have proposed that patients with high pretest probability of diagnosis of OSA not undergo PSG but proceed directly to CPAP titration either in the laboratory or unattended with an autotitration device (Flemons et al. 2003; Masa et al. 2004; Mulgrew et al. 2007 mentioned above).

Fitzpatrick et al. (2003) reported similar outcomes between standard laboratory-based CPAP titration and patient self-titration in CPAP-naïve subjects. Eighteen CPAP-naive patients (16 males, 50 ± 15 years old, apnea hypopnea index 40 ± 20 with a new diagnosis of OSA) were tested. Testing was performed before and after CPAP treatment in each of two 5-week study limbs. Compliance with CPAP treatment, the Sleep Apnea Quality of Life Index, the Functional Outcomes of Sleep Questionnaire score, ESS score, sleep architecture, sleep apnea and maintenance of wakefulness tests were measured. Both modes of CPAP treatment significantly improved objective subjective measures of OSA, but they did not differ in efficacy. The authors concluded that home self-titration of CPAP is as effective as in-laboratory manual titration in the management of patients with OSA.

Hukins (2005) also evaluated the use of low arbitrary pressure CPAP before formal CPAP titration to determine if arbitrary pressure CPAP is equivalent to formal CPAP in terms of compliance and improvements in subjective sleepiness and quality of life. Using an open-labeled, randomized, parallel design, 93 subjects were randomized to start CPAP either after a CPAP titration sleep study (study-determined pressure) or at an arbitrary pressure before the treatment sleep study (arbitrary-pressure CPAP). Primary outcome included ESS scores and secondary outcomes were objective compliance, quality of life and the visual analog (VAS) scale of subjective feelings towards CPAP therapy. The results of the study revealed that although there were no differences in CPAP compliance, side effects, SF-36 parameters or ESS scores, there was significantly higher sleep efficiency (proportion of sleep in the period potentially filled by sleep- i.e. the ratio of total sleep time to time in bed) in the arbitrary -pressure group compared to the study-determined CPAP pressure group. The author also noted that subjects who were unable to tolerate CPAP were identified by the use of arbitrary pressure. This led to a reduction in the proportion of "wasted" PSGs; i.e. studies performed in subjects not persisting with treatment. According to the author, a limitation of the study was the fact that the results are not well generalizable to the Medicare population since the average age in both groups was close to 50 years.

Other Diagnostic Strategies

Rice et al. (2006) piloted a study to evaluate unattended cardiopulmonary (CP) sleep studies as a diagnostic and treatment tool for patients with OSA. After all 106 subjects were initially evaluated by a pulmonary physician to identify those with a high risk of OSA, an ESS was administered. Those who were felt to have a high suspicion of OSA were offered either a PSG (which could take up to 6 months to schedule), or an unattended CP sleep study. Patients electing to use the unattended CP sleep study were lodged as outpatients overnight in the medical center. The diagnostic portable system used was the Embletta PDS, which included an oral thermometer, a nasal flow sensor, a snore microphone, a pulse oximeter, and strain gauges for thoracic and abdominal expansion. AHI was the outcome of interest. Patients with a positive CP test (an AHI of 5 events per hour or greater) were sent home with a REMstar auto CPAP system and a mask that was custom-fitted by a trained respiratory therapist.

After using auto CPAP nightly for a week (REMstar auto CPAP system adjusted to the patient's pressure needs by analyzing the shape curve of his/her airflow signal and peak flow), patients were then issued a home CPAP machine with settings based on the pressure that was found to be effective for at least 90% of the trial patients. ESS scores were measured at baseline and after 6 months of home CPAP use. Patients who had been prescribed home CPAP were assessed for global sleepiness at 12 months. CP studies were performed on 106 patients, all participants were males (mean age 59.9±10.1), mean BMI of 33.5 and mean ESS score (reference) of 13.1 ± 5.2. Of the 106 original patients, auto CPAP was initiated on 92 subjects. Based on the results of the one week auto CPAP, home CPAP was initiated on 84 patients. According to the authors, "among our patients, improvement in OSA symptoms and long-term adherence to prescribed CPAP was similar to published reports of patients who had undergone conventional PSG testing." At 6 months follow-up, 98% of CPAP patients were available; ESS scores at baseline and follow up were 14±4.6 and 10±5.6 (p=0.001), and adherence to CPAP usage was 84%.

Limitations of the study included the lack of confirmatory PSG to determine rate of false positives (but the mean AHI from this study was similar to that reported in published series of patients who had PSGs; and the absolute magnitude of ESS score improvement in this study was similar to that reported for patients who were prescribed CPAP after a PSG). Other limitations are the inability to calculate the diagnostic accuracy of a negative CP study for OSA; the fact that all subjects were male; and that adherence to prescribed CPAP was not based on objective data but rather on self-reporting.

CPAP Harms

A thorough review of the literature yielded almost no data on any harm from CPAP. One German paper (Fietze et al. 1996) reported on 9 patients with an increase of central apneas. Because of this complication, a rapid optimization of the respiratory pressure or a change to nBiPAP (nasal bilevel pressure support ventilation) therapy was necessary in five of the patients. Two of the patients showed cardiac arrhythmias, some of which were severe. One patient produced a remarkable central hypoventilation during the initial phase of CPAP-therapy. The nBiPAP-titration combined with right-heart catheter monitoring could demonstrate in another patient a possible cardiac decompensation through an increased ventilatory pressure. The authors concluded that the risk of positive-pressure ventilation is higher in patients with accompanying cardiac, pulmonary, neuropsychiatric and/or otorhinolaryngologic disorders. They suggested an intensive "apparative" [sic] monitoring as well as staff supervision during the introduction to a respiratory treatment in those patients. They believe that if complications from CPAP appear, a rapid optimization of the ventilatory pressure or a change to another respiratory treatment is indicated.

4. MedCAC

CMS convened the MedCAC on September 12, 2007 to consider questions pertinent to this reconsideration. The questions were appended to the proposed decision memorandum and we refer the interested reader to that document. We are not reiterating them here due to the length of this document. Additional information about the meeting can be found at: https://www4.cms.hhs.gov/mcd/viewmcac.asp?where=index&mid=40.

The MedCAC expressed moderate to high confidence that there was sufficient evidence to determine if clinical evaluation combined with PSG can, in routine use, produce an accurate diagnosis of OSA for the prescription of CPAP. Moderate confidence was expressed on the evidence for clinical evaluation combined with home sleep testing. Less confidence was expressed on the evidence for clinical evaluation used alone.

Considering the evidence on the ability of various diagnostic strategies to correctly identify patients with OSA and exclude patients who do not have OSA, the MedCAC expressed the following levels of confidence.

Clinical evaluation combined with PSG: strong moderate to high
Clinical evaluation combined with Type 2 home sleep testing: strong moderate

Clinical evaluation combined with Type 3 home sleep testing: moderate
Clinical evaluation combined with Type 4 home sleep testing: less than moderate
Clinical evaluation alone: less than moderate

The MedCAC did not provide a formal consideration of home sleep testing strategies that would employ clinical evaluation in combination with an unclassified device, i.e. not within Types 1-4.

The MedCAC decided not to address which clinical factors should be included in the clinical evaluation.

Considering the evidence on the ability of various diagnostic strategies to predict successful use of CPAP, the MedCAC expressed moderately high confidence in clinical evaluation combined with PSG; moderate confidence in clinical evaluation combined with home sleep testing; low to moderate confidence in clinical evaluation combined with a trial of CPAP; and low confidence in clinical evaluation alone.

The MedCAC expressed low to moderate confidence that the strategy of a trial by CPAP would not produce clinically meaningful harm. The concerns about potential harm relate to the possibility of missing the diagnosis of non-OSA pathology rather than concerns about CPAP itself.

The MedCAC expressed low to moderate confidence that its conclusions could be generalized to the Medicare population or to community based providers.

5. Evidenced based Guidelines

A November 14, 2007 search of http://www.guidelines.gov/ produced several guidelines relevant to CPAP or OSA in adults. All had been published or updated since 2003. Portions speaking to the questions posed in this memorandum were excerpted and were included in the proposed decision memorandum. We refer the reader to that document and will not reiterate them here in consideration of the length of this final decision memorandum. We note that the American Academy of Sleep Medicine (AASM) revised its guidelines while this NCA was open. We summarize that revision below since it was not discussed in the proposed decision memorandum.

American Academy of Sleep Medicine

Clinical guidelines for the use of unattended portable monitors in the diagnosis of OSA in adult patients. Portable Monitoring Task Force of the American Academy of Sleep Medicine. Collop NA, Anderson WM, Boehlecke B, Claman D, Goldberg R, Gottlieb DJ, Hudgel D, Sateia M, Schwab R; Portable Monitoring Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med. 2007 Dec 15;3(7):737-47.

Based on a review of literature and consensus, the Portable Monitoring Task Force of the American Academy of Sleep Medicine (AASM) makes the following recommendations: unattended portable monitoring (PM) for the diagnosis of OSA (OSA) should be performed only in conjunction with a comprehensive sleep evaluation. Clinical sleep evaluations using PM must be supervised by a practitioner with board certification in sleep medicine or an individual who fulfills the eligibility criteria for the sleep medicine certification examination. PM may be used as an alternative to polysomnography (PSG) for the diagnosis of OSA in patients with a high pretest probability of moderate to severe OSA. PM is not appropriate for the diagnosis of OSA in patients with significant comorbid medical conditions that may degrade the accuracy of PM. PM is not appropriate for the diagnostic evaluation of patients suspected of having comorbid sleep disorders. PM is not appropriate for general screening of asymptomatic populations. PM may be indicated for the diagnosis of OSA in patients for whom in-laboratory PSG is not possible by virtue of immobility, safety, or critical illness. PM may also be indicated to monitor the response to non-CPAP treatments for sleep apnea. At a minimum, PM must record airflow, respiratory effort, and blood oxygenation. The airflow, effort, and oximetric biosensors conventionally used for in-laboratory PSG should be used in PM. The Task Force recommends that PM testing be performed under the auspices of an AASM-accredited comprehensive sleep medicine program with written policies and procedures. An experienced sleep technologist/technician must apply the sensors or directly educate patients in sensor application. The PM device must allow for display of raw data with the capability of manual scoring or editing of automated scoring by a qualified sleep technician/technologist. A board certified sleep specialist, or an individual who fulfills the eligibility criteria for the sleep medicine certification examination, must review the raw data from PM using scoring criteria consistent with current published AASM standards. Under the conditions specified above, PM may be used for unattended studies in the patient's home. A follow-up visit to review test results should be performed for all patients undergoing PM. Negative or technically inadequate PM tests in patients with a high pretest probability of moderate to severe OSA should prompt in-laboratory polysomnography.

The AASM makes the following recommendations on the use of CPAP with the level of recommendation in parenthesis:

Standard *- This is a generally accepted patient-care strategy, which reflects a high degree of clinical certainty. The term standard generally implies the use of Level I Evidence, which directly addresses the clinical issue, or overwhelming Level II Evidence.*
Guideline *- This is a patient-care strategy, which reflects a moderate degree of clinical certainty. The term guideline implies the use of Level II Evidence or a consensus of Level III Evidence.*
Option *- This is a patient-care strategy, which reflects uncertain clinical use. The term option implies either inconclusive or conflicting evidence or conflicting expert opinion.*

Treatment with continuous positive airway pressure (CPAP) must be based on a prior diagnosis of OSA (OSA) established using an acceptable method (Standard).

CPAP is indicated for the treatment of moderate to severe OSA (Standard).

CPAP is recommended for the treatment of mild OSA (Option).

CPAP is indicated for improving self-reported sleepiness in patients with OSA (Standard).

CPAP is recommended for improving quality of life in patients with OSA (Option).

CPAP is recommended as an adjunctive therapy to lower blood pressure in hypertensive patients with OSA (Option).

Full-night, attended polysomnography performed in the laboratory is the preferred approach for titration to determine optimal positive airway pressure; however, split-night, diagnostic-titration studies are usually adequate (Guideline).

CPAP Usage should be objectively monitored to help assure utilization (Standard).

Close follow-up for positive airway pressure (PAP) usage and problems in patients with OSA by appropriately trained health care providers is indicated to establish effective utilization patterns and remediate problems, if needed. This is especially important during the first few weeks of PAP use (Standard).

The addition of heated humidification is indicated to improve CPAP utilization (Standard).

The addition of a systematic educational program is indicated to improve PAP utilization (Standard).

After initial CPAP setup, long-term follow-up for CPAP-treated patients with OSA by appropriately trained health care providers is indicated yearly and as needed to troubleshoot PAP mask, machine, or usage problems (Option).

CPAP and bi-level positive airway pressure (BPAP) therapy are safe; side effects and adverse events are mainly minor and reversible (Standard).

While the literature mainly supports CPAP therapy, BPAP is an optional therapy in some cases where high pressure is needed and the patient experiences difficulty exhaling against a fixed pressure or coexisting central hypoventilation is present (Guideline).

BPAP may be useful in treating some forms of restrictive lung disease or hypoventilation syndromes associated with daytime hypercapnia (Option).

6. Professional Society Position Statements

American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)
The AAO-HNS is the requestor of record for this reconsideration and supports extension of Medicare coverage of OSA diagnosis to portable HST devices.

The American Association for Respiratory Care (AARC)
The AARC recommends that CMS revise its coverage policy to require sleep testing to be performed in accredited facilities with accreditation to be determined by CMS. In addition, AARC recommends that any new device introduced into the home for sleep testing should meet minimum testing criteria. For example, central apnea versus obstructive apnea requires more physiologic data than pulse oximetry and flow. AARC further recommended and suggested language that CMS specify the types of personnel that are qualified to provide home testing.

The American College of Chest Physicians (ACCP)
The ACCP concluded that additional research is needed addressing clinical outcome in a variety of age and ethnic populations that reflect society before this NCD can be revised.

The American Academy of Sleep Medicine (AASM)
The AASM requested that CMS not change its NCD on CPAP therapy for OSA to allow diagnosis based on portable monitoring. The AASM supports a modification of the two hour rule based on expert opinion and not evidence.

7. Expert Opinion

CMS did not seek outside expert opinion beyond the TAs and the MedCAC. However, many experts provided their opinions as comments or position statements which are considered in the relevant sections of this memorandum.

8. Public Comments

Initial comment period 3/14/2007 – 4/13/07

As noted above CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum. CMS responses to initial comments are, as customary, incorporated into our analysis.

CMS received a total of 717 comments during the initial public comment period. Thirty-seven (5%) of the 717 comments were duplicates, resulting in 680 actual comments. Commenters included organizations, manufacturers and suppliers, physicians and other clinicians, and patients. One hundred-seventy comments were generated by an industry-sponsored write in campaign. Many stakeholders came in for face-to-face meetings with CMS staff members and also submitted formal comments. Fifty-seven percent (388/680) of the commenters (including all 170 write-in comments) agreed with the requestor and supported expansion of Medicare coverage to include the use of HST for the identification of beneficiaries eligible for CPAP. Forty-three percent (292/680) disagreed with the requestor.

Only 32 commenters expressed an interest in the trial use of CPAP without a sleep study test. One commenter recommended that the patient be allowed to have a trial period on CPAP therapy for 2 to 3 days before allowing Medicare coverage for CPAP therapy. Ten comments supported revision of the requirement for 2 hours of recorded sleep.

Many commenters questioned the motives of parties whose opinions differed from their own. Specifically, some commenters alleged that economic self-interest had led to selective consideration of evidence in support of particular opinions or guidelines.

Second comment period 12/14/2007-1/13/2008

CMS received a total of 300 timely public comments during the second comment period. Most comments were not accompanied by published scientific evidence. Listed below is a summary of the comments received and CMS' response:

Agrees with CMS proposed decision

Comment
Many commenters expressed support for all or parts of the proposed decision. They noted that Medicare coverage of home sleep studies to diagnose OSA to qualify for CPAP therapy will improve access to care and that home sleep tests are more accurate since you sleep more naturally in the home setting.

Response
CMS appreciates the support for the proposed decision.

Disagrees with some or all of CMS' proposed decision

Comment

Commenters questioned the integrity of the OSA treatment in the community and cautioned those involved in the decision making not to overlook the potential for abuse and not to allow this technology to be unleashed until adequate guidelines are available for appropriate utilization by qualified physicians. Some commenters believe this policy change will further degrade the current trend of inappropriate CPAP titrations and poor compliance.

Response
We are aware that there is the potential for abuse with this expansion of coverage, and we are taking steps to minimize the vulnerability of the Medicare program. These safeguards may include strategies beyond this NCD and rely on separate authorities. We believe that the education requirements for CPAP will support the appropriate provision of this benefit. As we noted elsewhere in this document we believe that CMS regulations require that diagnostic tests be performed with an appropriate level of supervision. We recognize that the polarization of the national stakeholder community makes it difficult at the national level to distinguish legitimate concerns from comments that may be motivated entirely by financial or business considerations. Medicare contractors may develop local strategies to ensure that these services are only provided in a manner consistent with the NCD and with applicable regulation.

Comment
Some commenters disagreed with the proposed coverage of the Watch-PAT100 under the CED paradigm. They claim that the Watch-PAT100 is a useful diagnostic tool and should not be distinguished from other HST devices.

Response
We agree. CMS has in the final decision removed the CED requirement for the use of the Watch-PAT100 HST device for the purposes of this NCD. This is a three channel device and we will treat it as a Type IV device under the NCD.

Comment
Some commenters note the risk of trying to identify and treat OSA patients without a complete PSG, risk of missing other diagnosis. Others questioned the use of HST in patients with particular comorbidities such as Parkinson’s Disease, chronic obstructive pulmonary disease (COPD) and others. Some commenters support the use of HSTs for those patients with a high pre test probability of OSA and no evidence of other sleep disorders.

Response
As we discussed in the proposed decision, no test is perfect for OSA diagnosis. It is important to note that we are not requiring that HST be done in the place of PSG. If the beneficiary's treating physician has good reason to believe that HST will be inadequate diagnostic tool for the beneficiary's condition, we expect that the physician would order a PSG rather than HST. Similarly, if the beneficiary's treating physician has good reason to believe that the result of an HST is insufficient in light of the beneficiary's clinical findings a subsequent PSG could be performed. We emphasize here that we expect that such retest decisions would be made on a case by case basis and we are not suggesting that the routine use of a two test routine would be reasonable and necessary.

Comment
Some commenters addressed issues other than the provisions of the proposed policy, for example the effect of past CMS policies and the anticipated effect of this policy on their business income.

Response
We appreciate that conditions in NCDs may have an impact on various business entities. Still, under Section 1862(a)(1)(A) our primary focus is on the health care of Medicare beneficiaries.

Comment
Some commenters claim that automatic sleep study scoring without the ability to review, edit, and confirm validity of raw data must not be allowed.

Response
The commenter did not submit any addition peer reviewed medical literature to support this statement. Thus, we are not making a determination on the use of automatic scoring in this NCD. However, we remind the reader of CMS regulations on diagnostic tests and the important role of the treating physician and other practitioners under this benefit.

Comment
Several commenters made note of CMS instructions via materials other than the NCD regarding sleep testing. In October CMS ruled that patients must be monitored by a registered polysomnographic technologist in sleep laboratories. Some find it “amusing” that CMS ruled that attended sleep studies could not be performed in a hotel or motel setting starting 1/1/2008, yet considering unattended studies for OSA in patients home.

Response
Entities that submit claims for Medicare payment may be subject to operational requirements on staffing, physical facilities or other factors. Thus, for example, a sleep laboratory may have to meet Medicare requirements for laboratory facilities. As the provisions in question are not part of this NCD we will not address them in this memorandum.

Comment
Some commenters noted that some patients may have difficulty performing the test at home without assistance.

Response
CMS agrees with this comment. We expect that the treating physician will consider this possibility when recommending HST rather than PSG.

Comment
A number of commenters suggest that the evidence is not generalizable to the Medicare population and to non-specialist providers.

Response
While the generalizability of the evidence is less than perfect, we do note that the MedCAC scoring on this issue was in the low to moderate range, thereby indicating some confidence in the generalizability of the evidence.

Comment
A commenter suggested that CPAP could help diagnose OSA

Response
We agree that there may be promise in this approach, but we have determined that the evidence does not yet fully support such use and we will only cover this use in the context of CED.

Comment
Studies have not been evaluated in the pediatric population, thus home studies should not be used in this population.

Response
Pediatric patients are, in general, not Medicare beneficiaries. We remind the reader that the diagnostic requirements of this policy are specific to adults.

Comment
Some commenters say that surgery will not necessarily correct the sleep problem, and that this will entail more diagnostic testing and possible more CPAP usage. They believe that this will increase Medicare spending.

Response
CMS has deleted from this decision the requirement that surgery be an alternative to the use of CPAP. While we appreciate the commenters point, we will not speculate on the effect of this NCD on the success or failure of surgical treatment nor on the impact of the new NCD on future Medicare spending..

Comment
HST should be considered for preliminary screening for OSA or done away with all together.

Response
We believe that the evidence supports the use of most HST diagnostic testing as alternatives to PSGs. We are not providing coverage of preliminary screening tests for beneficiaries in the absence of any signs or symptoms of OSA. Coverage of purely screening tests (not diagnostic tests) are established pursuant to specific legislation (e.g. screening mammography, screening for glaucoma, etc.)

Partially Agrees with CMS' decision

Comment
Some commenters asked us to narrow the scope on types of allowable HST, generally to restrict the use of Type IV devices for the purposes of this NCD.

Response
CMS considered this comment in the development of the final decision. We also note that the MedCAC expressed less confidence about the evidence on the diagnostic usefulness of Type IV HST than other types. Thus, we have provided coverage for CPAP when the OSA is diagnosed via a Type IV device only when the Type IV device measures three or more channels.

Comment
Some commenters claim that compliance with the CPAP is largely successful because of intervention from sleep technicians being able to work with the patient.

Response

While we have not reviewed robust evidence speaking to the specific value of the sleep technician in this regard, we are not suggesting the opposite. We anticipate the providers furnishing the HST will want to maximize the efficiency of testing and minimize the occurrences of failed tests, i.e. tests that are invalid due to faulty test technique. Thus we anticipate that they will provide education to teach the beneficiary to administer the HST and be available to assist the patient with the HST.

Comment
Some commenters say that test equipment can come off and patients will not recognize it. This would necessitate a retest.

Response
During the initial clinical evaluation the patient's treating physician must assess whether the patient is capable of successfully fulfilling his or her role in the completion of a HST. An improperly performed test can be differentiated from a test that was performed in a technically correct manner but which is falsely positive or negative for other reasons.

Comment
Some commenters claim that a12 week period of initial CPAP use is not adequate to determine if the patient will use and benefit from CPAP. Others proposed specific criteria to determine use and benefit. The AASM proposes the use of specific guidelines such as CPAP adherence for at least 4 hours of sleep for at least 70% of the days or an improvement in clinical symptoms. Other commenter's recommend the use of outcome measures to assess benefit.

Response
The evidence indicates that a 12 week period is sufficient for this purpose. So long as they do not conflict with the NCD, Medicare contractors may develop additional policies for determining the necessary improvement in the beneficiary's OSA as a result of using CPAP.

Clarification requested on CMS' decision

Comment
Some commenters asked whether IDTFs (Independent Diagnostic Testing Facilities can provide HSTs.

Response
We are not making a specific determination about IDTFs in this decision.

Comment
Some commenters asked what documentation will be required to support claims for services provided in the context of this NCD.

Response
We expect that the treating physician's contemporaneous medical record documentation will be adequate to describe the beneficiary's condition for services provided in the context of OSA treatment. Medicare contractors may determine what documentation may be required for their review of claims.

Comments with evidence

Comment
A number of comments with references to journal articles were submitted.

Response

The majority reiterated data that we had considered or submitted references on topics that were tangential to the scope of our decision One commenter added references on CPAP harms (Krieger et al 1983, Teschler et al. 1995, Piper et al. 1995) reiterating and reinforcing the little data we had on CPAP harms. These data recommended taking special care with CPAP use and treatment in patients with cardiopulmonary disease. We believe that these data are consistent with our proposed decision so we are not making any changes as a result of this evidence.

VIII. CMS Analysis

NCDs are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Act. § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items and services must be "reasonable and necessary" for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. § 1862(a)(1)(A).

In addition to section 1862(a)(1)(A) of the Act, a second statutory provision may permit Medicare payment for items and services in some circumstances. That statute, section 1862(a)(1)(E) of the Act, provides, in pertinent part, that:
(a) Notwithstanding any other provision of this title, no payment may be made under part A or part B for any expenses incurred for items or services—
. . .
(E) in the case of research conducted pursuant to section 1142, which is not reasonable and necessary to carry out the purposes of that section[.]
. . .

Section 1142 of the Act describes the authority of the AHRQ. CMS has described this statute more fully in a Guidance Document available at https://www.cms.hhs.gov/ncpc_view_document.asp?id=8. See also section 310 Medicare NCD Manual.

Under the authority of section 1862(a)(1)(E) of the Act, CMS may pay for items and services furnished in connection with certain medical research. Coverage is conditioned on care being delivered in a setting with a pre-specified data collection process and additional protections in place such as are present in some research studies. Under section 1142 of the Act, research may be conducted on the outcomes, effectiveness, and appropriateness of health care services and procedures to identify the manner in which diseases, disorders, and other health conditions can be prevented, diagnosed, treated, and managed clinically. In addition, evaluations of the comparative effects, health and functional capacity; alternative services and procedures utilized in preventing, diagnosing, treating, and clinically managing diseases, disorders, and other health conditions may be conducted.

In rare instances, for some items or services, CMS may determine that the evidence is very preliminary and not reasonable and necessary for Medicare coverage under section 1862(a)(1)(A) of the Act, but, if the following criteria are met, coverage with study participation might be appropriate:

a. The evidence includes assurance of basic safety;
b. The item or service has a high potential to provide significant benefit to Medicare beneficiaries; and
c. There are significant barriers to conducting clinical trials.

These research studies will be rigorously designed and include additional protections and safety measures for beneficiaries.

To qualify for reimbursement, such a study must be designed to produce evidence that could be used in a future NCD that would focus on whether the item or service should be covered by Medicare under 1862(a)(1)(A) of the Act. Payment for the items and services provided in the study will be restricted to the Medicare qualified patients involved as human subjects in the study.

Consistent with section 1142 of the Act, AHRQ supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

REVIEW OF THE EVIDENCE

A number of issues have emerged during our review of the evidence. Some physicians express concern about the lack of timely access to PSGs while others argue that access is not problematic; stakeholders debate the comparable accuracy of home apnea monitoring and PSGs; and recent research suggests that neither PSG nor HST may be needed for the diagnosis of CPAP-responsive OSA in selected patient populations. Paradoxically, some patients' OSA symptoms may be so severe that they cannot sleep for a sufficient continuous duration to complete a PSG. Adding to the complexity of our review, the stakeholder community itself is clearly polarized into opposing camps.

The relevance of OSA diagnosis is founded on the long term morbidity and mortality that have been observed in patients who display a particular constellation of symptoms, signs and test results. Absent that morbidity and mortality, a self-limited apneic episode in and of itself appears of little consequence. Hence the challenge is to select for long term CPAP treatment only those patients who will benefit from OSA therapy, against a background of persons who may for various reasons have a normal or abnormal test on a given night.

It is important to state at the outset that sleep testing, whether via PSG or HST, is used to confirm or refute a clinical suspicion of OSA. In other words, we have no evidence that physicians refer "normal" patients, i.e. patients who manifest no symptoms or signs of OSA, for sleep testing. Sleep testing does not occur in a vacuum, divorced from the overall clinical evaluation. We also note that while this NCD speaks to the diagnosis of OSA in the context of Medicare coverage of CPAP devices, we are not establishing coverage criteria for the diagnosis of OSA for other purposes, such as the coverage of other OSA treatments. Nor are we addressing the use of sleep testing to diagnose conditions other than OSA. Hence the accurate identification of Medicare beneficiaries who will respond clinically to CPAP is at the heart of this review and analysis.

PSG is utilized as a reference standard in many clinical trials; however, we do not believe it is a true gold standard. In a circular argument, the test result has been incorporated into the diagnosis of the disease itself. In the absence of a pathologic gold standard, this is an understandable though not ideal concession to practicality. The accuracy and precision of PSG may be compromised by many factors such as inter-reader variability, the use of different test instruments, night to night variability in a given patient, and patient ability to sleep in a non-home setting. Even if all these variables are controlled, the PSG test itself has not been proven to identify all true cases of OSA, i.e. those persons who will develop OSA-associated morbidity and mortality if untreated.

Therefore, when PSG is performed and read with a threshold of AHI $\geq$ 15 events per hour for OSA, the sensitivity for detecting a true case of OSA is not known. Neither is its specificity for detecting those who do not have OSA truly known. An AHI suggestive of OSAHS does not conclusively identify those patients who will benefit from treatment. Since the true sensitivity and specificity of PSG are uncertain and the reported agreement between HST and PSG is not complete, we are concerned that a significant number of true cases of OSA are not detected by either test. We are also faced with evidence that some patients who test positive for OSA do not appear to respond appropriately to CPAP therapy, in some cases due to poor compliance with CPAP use.

Question 1: Is the evidence adequate to determine that diagnostic strategies other than facility based PSG accurately identify patients with OSA who will benefit from CPAP treatment?

We note evidence from our internal assessment and from the AHRQ TAs that HST devices may, with high positive likelihood ratios (> 10) and low negative likelihood ratios (< 0.1), identify patients who have AHIs suggestive of OSAHS. Although there is published data comparing HST with PSG, in the absence of a true gold standard it is challenging to categorize the discrepancies as errors.

The body of evidence pertinent to the use of HST devices for the diagnosis of OSA is significantly more robust than when we last considered this NCD. This is supported by the more favorable September 2007 MedCAC scores for HST compared to the September 2004 MCAC scores. Thus, we find that the evidence is sufficient to conclude that, in appropriately selected patients, some HST monitors will identify a significant proportion of patients with OSA who will respond clinically to CPAP and will exclude a significant proportion of those who will not.

CMS also reviewed oximetry alone for the diagnosis of sleep apnea. There was limited evidence and many of the authors recognized limitations of the studies. We believe the evidence reviewed does not demonstrate its utility in the diagnosis of OSA, and we cannot be confident that this diagnostic modality accurately identifies those patients with OSA who will respond clinically to CPAP and excludes those who will not.

The TA analyzed Type IV monitors with three or more channels separately from those with only one or two channels. The quality of the evidence on the former is described as higher than on the latter. We also note that the TA did not include all Type IV monitors.

"…However, especially for type IV devices, we excluded the few studies that did not measure directly at least one respiratory signal or the O2 saturation. Thus, studies using only static charge-sensitive mattresses, only Holter recordings for heart rate, or studies that used only analysis of snoring sounds were excluded. Similarly, we excluded studies that that used pulse oximetry but analyzed only the variability of the heart rate (i.e., used oximetry in lieu of ECG to detect pulse rate) and did not evaluate O2 saturation patterns. In general, monitors that did not record a respiratory signal or SaO2 during sleep rely on "indirect" assessment of respiratory disturbances in people suspected for OSAHS, and most often were described in older studies. The frequency of respiratory disturbances is a key issue in the diagnosis of OSAHS, and is assessed by the vast majority of modern monitors."

In light of the lack of evidence of utility for oximetry and its classification as a Type IV device, as well as the TA finding of greater diagnostic accuracy in Type IV monitors with three or more channels, we have reevaluated our proposed conclusion to cover CPAP based on OSA diagnosis via Type IV devices as a group. We believe our evidence review demonstrates that single channel devices, such as oximetry, are not adequate to identify appropriate candidates for CPAP. Thus, we are modifying our proposed decision and will, with regards to the use of Type IV HST for the diagnosis of OSA, only cover CPAP when the diagnosis of OSA includes a positive test with Type IV device measuring at least three channels.

CMS separately reviewed evidence on the use of the Watch-PAT100 device (see above), a multichannel device that measures PAT. The conclusions that can be confidently drawn from the evidence, while mildly constrained by methodologic limitations (sample and subject selection, sample size, non-consecutivity of subjects, confounders not accounted for, and combining results of different types of patients in analysis), are of similar strength as that available for many of the type IV devices in the TA and, therefore, we consider the Watch-PAT100 as a three channel Type IV device for the purposes of this decision.

Even though the evidence we reviewed was not adequate to support oximetry testing alone under § 1862(a)(1)(A), some of the evidence does suggest a benefit. Thus, we have determined to cover CPAP for beneficiaries with the diagnosis of OSA based on the results of a diagnostic procedure other than PSG or Type II, Type III, or Type IV measuring at least three channels for HST only in the context of a clinical study that meets the criteria approved by AHRQ and reported at #6 of this decision.

Even though we believe the evidence supports using PSG or HST for diagnosis of OSA, the evidence also demonstrates that many patients with a positive PSG or HST do not benefit from CPAP. We do, however, have evidence from an RCT (Mulgrew 2007) that a trial period of up to 12 weeks of CPAP after the initial diagnosis is beneficial in identifying those beneficiaries who positively respond to CPAP. The evidence indicates that patients who do not have true OSA (false positives) will quickly reject CPAP treatment in practice and will not be harmed by a short exposure to CPAP. Moreover, in our final decision we are only providing coverage of CPAP beyond twelve weeks for those beneficiaries that have a positive clinical response to CPAP.

Question 2: Is the evidence adequate to determine that the accurate diagnosis of OSA requires at least two hours continuous recorded sleep?

We could find no rigorous evidence associating diagnostic accuracy with continuous sleep time recording of at least two hours duration. We are also confronted with reasonable arguments that patients with the most severe OSA are in practice incapable of continuous sleep of two hours duration. Therefore, we have determined that the answer to Question 2 is no. However, the current standards of requiring a rate of $\geq$ 15 events/hour over two hours for less symptomatic patients and 5 through 14 events/hour over two hours for more symptomatic patients do require a minimum number of events. For example, a patient who has at least 15 recorded events per hour over a two hour period would have had at least 30 recorded events. Thus, while we no longer believe two continuous hours of recorded sleep are always necessary, we will continue to require that the total number of events needed for a positive test to be that which would need to occur over two hours to arrive at the specified rates in the current NCD. That is, recording of at least 30 events for patients without comorbidities and at least 10 events for patients with comorbidities is required for the computation of events per hour. The effect of this change is to permit coverage of CPAP in those beneficiaries whose OSA was paradoxically too severe to permit successful completion of the test under the previous NCD without removing coverage for beneficiaries who would have met the requirements of the previous NCD.

Question 3: Is diagnosis of OSA by clinical criteria alone sufficient for the use of CPAP in the absence of either a positive PSG or a positive unattended multichannel HST?

The published literature on both PSG and HST for OSA diagnosis reflects the results of clinical studies enrolling subjects referred by a medical provider for a test based on clinical suspicion of OSA. Those providers likely made the referral because the subject presented with one or more symptoms or signs such as snoring, daytime sleepiness, witnessed apneic episodes, a thick neck, a higher BMI, or a positive sleep questionnaire, to mention some possibilities. If a patient with clinically suspected OSA undergoes PSG or HST, the patient is referred for CPAP if the PSG is positive. The evidence indicates that both of these strategies result in an unknown number of false positive and false negative diagnoses.

There is evidence, albeit limited, to support the use of CPAP in lieu of PSG or HST in the diagnosis of OSA. This is based on the observation that patients with OSA are more tolerant of CPAP than patients who do not possess this condition, and that the use of CPAP does not result in untoward effects even in patients who do not have a diagnosis of OSA. The MedCAC expressed little confidence in the evidence currently available to support this use. We do not believe that this evidence is currently sufficient to definitely answer this question and we therefore have determined that the answer to Question 3 is no.

However, though the evidence we reviewed was not adequate to support coverage of CPAP under § 1862(a)(1)(A) based on a clinical evaluation alone for the diagnosis of OSA, some of the evidence does suggest a benefit. Thus, we will cover a clinical evaluation without sleep testing for the diagnosis of OSA in the context of a clinical study that meets the AHRQ criteria outlined at #6 of this decision.

Harms of CPAP

We found little evidence of harm attributable to CPAP. We recognize that the population that currently undergoes CPAP is somewhat narrower than all clinically suspected cases and that the generalizability of the current literature on harm may be poorly generalizable to populations beyond those that currently qualify for CPAP. Further, persons with co-morbidities associated with OSA may be at more risk than suspected. However there is limited evidence on this topic and thus we cannot confidently conclude that significant possible harm has in fact been excluded. In other words, the absence of evidence of harm does not reliably exclude the likelihood of harm if a methodologically rigorous assessment for harm has not been completed. Our concerns are shared by the MedCAC, which expressed low to moderate confidence that the strategy of a trial by CPAP would not produce clinically meaningful harm. Potential concerns about potential harm include the possibility of missing the diagnosis of non-OSA pathology in addition to concerns about potential harms attributable to CPAP itself

Summary

We have determined that the evidence is adequate to conclude that CPAP is reasonable and necessary under section 1862(a)(1)(A) of the Act for adult beneficiaries with OSA diagnosed by a clinical examination accompanied by a positive PSG, Type II HST, Type III HST or a Type IV HST measuring three of more channels. We are considering Watch-PAT 100 as a three channel Type IV device for the purposes of this decision. Since we have evidence that not all patients with a positive PSG or HST will benefit from CPAP, we are determining that CPAP is initially only reasonable and necessary for a period of 12 weeks to determine benefit from and compliance with this therapy. Coverage beyond that period is contingent on the beneficiary's OSA improving as a result of CPAP.

As we have not found rigorous evidence to support continuing the requirement for a minimum of two hours of continuous recorded sleep time, we have removed that requirement. We appreciate the supportive public comments on this point.

We are also deleting the language in the past NCD that required documentation of "moderate to severe OSA" and "surgery is a likely alternative" as a condition of CPAP coverage. We believe that they are no longer needed as stand alone requirements since we have outlined in very specific terms the requirements for a positive diagnosis.

We acknowledge the concerns that some of these patients who do not tolerate CPAP may have other conditions for which PSG or other testing may be indicated and we anticipate that a prudent physician would refer the patient for such testing if needed.

The evidence indicates that some risk factors for OSA are modifiable over time; for example, a patient may gain or lose weight, or resume or discontinue tobacco smoking. This raises two specific concerns. One, patients who initially have a true negative test may, years later, progress to more severe disease and may subsequently truly test positive. Second, patients who initially require CPAP may modify their underlying risk factors for OSA and improve to the point that further CPAP treatment is not required. We believe that these determinations are best made at this time by local Medicare contractors who can consider the medical information of the individual patient.

In general, CMS regulation at 42 CFR 410.32(a) requires that all diagnostic tests "…must be ordered by the physician who is treating the beneficiary, that is, the physician who furnishes a consultation or treats a beneficiary for a specific medical problem and who uses the results in the management of the beneficiary's specific medical problem. Tests not ordered by the physician who is treating the beneficiary are not reasonable and necessary..." There are some specific exceptions specified in the regulations.

For the purposes of this NCD on CPAP, we expect that the beneficiary's treating physician will assess the beneficiary and, if a reasonable suspicion of sleep apnea is indicated by those clinical findings, order appropriate sleep testing and use the results in the management of the beneficiary's condition to make or exclude a diagnosis of OSA. The initiation of home sleep testing or evaluation of the test results without a prior order from the beneficiary's treating physician would not be considered sufficient for the coverage of CPAP.

We recognize that diagnostic sleep testing is also used to aid the management of other conditions, e.g. narcolepsy and nocturnal seizures. This NCD does not speak to the characteristics of sleep testing to qualify Medicare beneficiaries for treatments other than CPAP for OSA.

As we discussed earlier in the decision memorandum, OSA has a spectrum of severity. Individual patients vary in their response to and adherence with CPAP treatment. Thus, the management of the beneficiary's specific medical problem, in this instance OSA, does not end with the initiation of CPAP treatment, and we expect that the beneficiary's response and adherence would be reflected in the contemporaneous medical record and adequate documentation will be available to support claims for Medicare payment.

CMS regulation at 42 CFR 410.32(b)(1) requires that diagnostic tests “…covered under section 1861(s)(3) of the Act and payable under the physician fee schedule must be furnished under the appropriate level of supervision by a physician as defined in section 1861(r) of the Act. Services furnished without the required level of supervision are not reasonable and necessary…” In the case of HST this is general supervision. Thus we expect that PSG and HST will be furnished with the appropriate level of supervision and we believe that local Medicare contractors may develop and implement local policies to ensure that claims are appropriately paid.

We remind the reader that suppliers of CPAP devices to Medicare beneficiaries are subject to regulatory requirements in addition to the coverage conditions of this NCD and that these requirements apply to physicians who supply DME. We note the following language as an example (72 FR 51019-51020 (9/5/07):

Response: In Phase II, we stated that the definition of "referral" excludes services personally performed or provided by the referring physician, but specifically includes any services performed or provided by anyone else *(69 FR 16063).* This interpretation is codified in the definition of "referral" at § 411.351. It is possible for a physician to order and personally furnish antigens to a patient and to order a refill for, and personally refill, an implantable pump. In such instances, there would be no "referral" for a designated health service, and no exception is needed.

We note that the furnishing of durable medical equipment (DME) and supplies by a referring physician requires a different analysis than the mere refilling of an implantable pump. There are few, if any, situations in which a referring physician would personally furnish DME and supplies to a patient, because doing so would require that the physician himself or herself be enrolled in Medicare as a DME supplier and personally perform all of the duties of a supplier as set forth in the supplier standards in § 424.57(c).

DME suppliers are entities that provide services under the specific Part B benefit for the provision of medical equipment and supplies for use in the patient's home. These entities must be enrolled with the appropriate Medicare contractor as a DME supplier and must meet all of the professional supplier standards and quality standards that we require through regulations and administrative or program instructions. The enrollment requirements and professional supplier standards are not waived in those situations in which a physician furnishes DME directly to the patient. The services to be personally performed by the physician would include, but not be limited to, the following, as appropriate

-
- Personally fit the item for the beneficiary;
- Provide necessary information and instructions concerning use of the DME;
- Advise the beneficiary that he or she may either rent or purchase inexpensive or routinely purchased DME;
- Explain the purchase option for capped rental DME;
- Explain all warranties;
- (Usually) deliver the DME to the beneficiary at home; and
- Explain to the beneficiary at the time of delivery how to contact the physician in his or her capacity as a DME supplier by telephone.

A referring physician claiming to provide DME personally would need to maintain adequate documentation to establish that the physician personally performed these and other required DME supplier activities. All of these supplier requirements would need to be satisfied in order for a physician to be considered to be providing personally DME items and supplies. This is true for all DME furnished by a physician, including, for example, continuous positive airway pressure (CPAP) equipment. We believe that it is highly unlikely that a referring physician would meet the criteria for personally performed services when dispensing CPAP or other DME equipment. Thus, the dispensing of CPAP equipment by a physician would almost always constitute a "referral" for purposes of the physician self-referral statute, as would the dispensing of CPAP equipment by anyone else affiliated with the referring physician, such as a nurse or physician assistant. We note that CPAP equipment is DME that does not qualify for the in-office ancillary services exception.

Finally, while we have not found adequate evidence to determine that CPAP is reasonable and necessary under § 1862(a)(1)(A) in beneficiaries who have a clinical diagnosis of OSA but have not had a positive PSG or a Type II, III, or IV (measuring three or more channels) HST , there is some evidence that suggests that other diagnostic tests or a clinical diagnosis alone may improve outcomes. Thus, we have determined that CPAP is covered in beneficiaries who have a clinical diagnosis of OSA but have not had a PSG or a Type II, Type III, or CMS recognized Type IV HST only when provided in a clinical study that meets the AHRQ requirements originally set forth in the proposed decision and finalized here at #6.

X. Conclusion

We received a request to reconsider the 2005 NCD for CPAP Therapy for OSA (CAG-00093R) to allow coverage of CPAP based upon a diagnosis of OSA by HST. After considering public comments and additional information, we are making the following changes to the NCD for CPAP. The revised indications and limitations NCD are noted in Appendix B.

1.

Coverage of CPAP is initially limited to a 12 week period for beneficiaries diagnosed with OSA as subsequently described. CPAP is subsequently covered for those beneficiaries diagnosed with OSA whose OSA improved as a result of CPAP during this 12 week period.

We remind the reader that DMEPOS suppliers are required to provide beneficiaries with necessary information and instructions on how to use Medicare-covered items safely and effectively. 42 CFR 424.57(c)(12). Failure to meet this standard may result in revocation of the DMEPOS supplier's billing privileges. 42 CFR 424.57(d).

2.

CPAP for adults is covered when diagnosed using a clinical evaluation and a positive:

a. polysomnography (PSG) performed in a sleep laboratory; or
b. unattended home sleep monitoring device of Type II; or
c. unattended home sleep monitoring device of Type III; or
d. unattended home sleep monitoring device of Type IV, measuring at least three channels

We remind the reader that, in general, pursuant to 42 CFR 410.32(a) diagnostic tests that are not ordered by the beneficiary's treating physician are not considered reasonable and necessary. Pursuant to 42 CFR 410.32(b) diagnostic tests payable under the physician fee schedule that are furnished without the required level of supervision by a physician are not reasonable and necessary.

3.

A positive test for OSA is established if either of the following criterion using the Apnea-Hypopnea Index (AHI) or Respiratory Disturbance Index (RDI) are met:

- AHI or RDI greater than or equal to 15 events per hour, or
- AHI or RDI greater than or equal to 5 and less than or equal to 14 events per hour with documented symptoms of excessive daytime sleepiness, impaired cognition, mood disorders or insomnia, or documented hypertension, ischemic heart disease, or history of stroke.

The AHI is equal to the average number of episodes of apnea and hypopnea per hour. The RDI is equal to the average number of respiratory disturbances per hour.

4.

If the AHI or RDI is calculated based on less than two hours of continuous recorded sleep, the total number of recorded events to calculate the AHI or RDI during sleep testing is at least the number of events that would have been required in a two hour period.

5.

We are deleting the distinct requirements that an individual have moderate to severe OSA and that surgery is a likely alternative.

6.

CPAP based on clinical diagnosis alone or using a diagnostic procedure other than PSG or Type II, Type III, or a Type IV HST measuring at least three channels is covered only when provided in the context of a clinical study when that study meets the following standards:

A clinical study seeking Medicare payment for CPAP provided to the beneficiary pursuant to Coverage with Evidence Development (CED) must address one or more of the following questions:

a. In Medicare aged subjects with clinically identified risk factors for OSA, how does the diagnostic accuracy of a clinical trial of CPAP compare with PSG and Type II, III & IV HST in identifying subjects with OSA who will respond to CPAP?

b. In Medicare aged subjects with clinically identified risk factors for OSA who have not undergone confirmatory testing with PSG or Type II, III & IV HST, does CPAP cause clinically meaningful harm?

The study must meet the following additional standards:

c. The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.
d. The research study is well-supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
e. The research study does not unjustifiably duplicate existing studies.
f. The research study design is appropriate to answer the research question being asked in the study.
g. The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
h. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 CFR Part 46. If a study is FDA-regulated, it also must be in compliance with 21 CFR Parts 50 and 56.
i. All aspects of the research study are conducted according to the appropriate standards of scientific integrity.
j. The research study has a written protocol that clearly addresses, or incorporates by reference, the Medicare standards.
k. The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life-threatening as defined in 21 CFR § 312.81(a) and the patient has no other viable treatment options.
l. The clinical research study is registered on the ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.
m. The research study protocol specifies the method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. However, a full report of the outcomes must be made public no later than three (3) years after the end of data collection.
n. The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria affect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.

o. The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Act, AHRQ supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions

APPENDIX A

General Methodological Principles of Study Design

(Section VI of the Decision Memorandum)

When making NCDs, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

Randomized controlled trials
Non-randomized controlled trials
Prospective cohort studies
Retrospective case control studies
Cross-sectional studies
Surveillance studies (e.g., using registries or surveys)
Consecutive case series
Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

APPENDIX B

Indications and Limitations of Coverage

B. Nationally Covered Indications

1. The use of CPAP is covered under Medicare when used in adult patients with Obstructive Sleep Apnea (OSA). Coverage of CPAP is initially limited to a twelve week period to identify beneficiaries diagnosed with OSA as subsequently described who benefit from CPAP. CPAP is subsequently covered only for those beneficiaries diagnosed with OSA who benefit from CPAP during this twelve week period.

2. The provider of CPAP must conduct education of the beneficiary prior to the use of the CPAP device to ensure that the beneficiary has been educated in the proper use of the device. A caregiver, for example a family member, may be compensatory, if consistently available in the beneficiary's home and willing and able to safely operate the CPAP device.

3. A positive diagnosis of OSA for the coverage of CPAP must include a clinical evaluation and a positive:
   a. Attended polysomnography (PSG) performed in a sleep laboratory; or
   b. unattended home sleep test (HST) with a Type II home sleep monitoring device; or
   c. unattended HST with a Type III home sleep monitoring device; or
   d. unattended HST witha Type IV home sleep monitoring device that measures at least three channels.

4. The sleep test must have been previously ordered by the beneficiary’s treating physician and furnished under appropriate physician supervision.

5. An initial twelve week period of CPAP is covered in adult patients with if either of the following criterion using the Apnea-Hypopnea Index (AHI) or Respiratory Disturbance Index (RDI) are met:

a. AHI or RDI greater than or equal to 15 events per hour, or
b. AHI or RDI greater than or equal to 5 and less than or equal to 14 events per hour with documented symptoms of excessive daytime sleepiness, impaired cognition, mood disorders or insomnia, or documented hypertension, ischemic heart disease, or history of stroke.

6. The AHI or RDI is calculated on the average number of events of per hour. If the AHI or RDI is calculated based on less than two hours of continuous recorded sleep, the total number of recorded events to calculate the AHI or RDI during sleep testing must be at a minimum the number of events that would have been required in a 2 hour period.

7. Apnea is defined as a cessation of airflow for at least 10 seconds. Hypopnea is defined as an abnormal respiratory event lasting at least 10 seconds with at least a 30 percent reduction in thoracoabdominal movement or airflow as compared to baseline, and with at least a 4 percent oxygen desaturation.
8.

Coverage with Evidence Development (CED): Medicare provides the following limited coverage for CPAP in adult beneficiaries who do not qualify for CPAP coverage based on criteria 1-7 above. A clinical study seeking Medicare payment for CPAP provided to a beneficiary who is an enrolled subject in that study must address one or more of the following questions

a. In Medicare aged subjects with clinically identified risk factors for OSA, how does the diagnostic accuracy of a clinical trial of CPAP compare with PSG and Type II, III & IV HST in identifying subjects with OSA who will respond to CPAP?
b. In Medicare aged subjects with clinically identified risk factors for OSA who have not undergone confirmatory testing with PSG or Type II, III & IV HST, does CPAP cause clinically meaningful harm?

The study must meet the following additional standards:

c. The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.
d. The research study is well-supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
e. The research study does not unjustifiably duplicate existing studies.

f. The research study design is appropriate to answer the research question being asked in the study.
g. The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
h. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 CFR Part 46. If a study is FDA-regulated, it also must be in compliance with 21 CFR Parts 50 and 56.
i. All aspects of the research study are conducted according to the appropriate standards of scientific integrity.
j. The research study has a written protocol that clearly addresses, or incorporates by reference, the Medicare standards.
k. The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life-threatening as defined in 21 CFR § 312.81(a) and the patient has no other viable treatment options.
l. The clinical research study is registered on the ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.
m. The research study protocol specifies the method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. However, a full report of the outcomes must be made public no later than three (3) years after the end of data collection.
n. The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria affect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.
o. The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

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